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Hydromorphone for cancer pain (Review)

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[Intervention Review]

Hydromorphone for cancer pain

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ABSTRACT

Background

This is an update of the original Cochrane Review first published in Issue 10, 2016. For people with advanced cancer, the prevalence of pain can be as high as 90%. Cancer pain is a distressing symptom that tends to worsen as the disease progresses. Evidence suggests that opioid pharmacotherapy is the most effective of these therapies. Hydromorphone appears to be an alternative opioid analgesic which may help relieve these symptoms.

Objectives

To determine the analgesic efficacy of hydromorphone in relieving cancer pain, as well as the incidence and severity of any adverse events.

Search methods

We searched CENTRAL, MEDLINE, Embase and clinical trials registers in November 2020. We applied no language, document type or publication status limitations to the search.

Selection criteria

We included randomised controlled trials (RCTs) that compared hydromorphone with placebo, an alternative opioid or another active control, for cancer pain in adults and children. Primary outcomes were participant-reported pain intensity and pain relief; secondary outcomes were specific adverse events, serious adverse events, quality of life, leaving the study early and death.

Data collection and analysis

Two review authors independently extracted data. We calculated risk ratio (RR) and 95% confidence intervals (CI) for binary outcomes on an intention-to-treat (ITT) basis. We estimated mean difference (MD) between groups and 95% CI for continuous data. We used a random-effects model and assessed risk of bias for all included studies. We assessed the evidence using GRADE and created three summary of findings tables.

Main results

With four new identified studies, the review includes a total of eight studies (1283 participants, with data for 1181 participants available for analysis), which compared hydromorphone with oxycodone (four studies), morphine (three studies) or fentanyl (one study). All studies

included adults with cancer pain, mean age ranged around 53 to 59 years and the proportion of men ranged from 42% to 67.4%. We judged all the studies at high risk of bias overall because they had at least one domain with high risk of bias.

We found no studies including children. We did not complete a meta-analysis for the primary outcome of pain intensity due to skewed data and different comparators investigated across the studies (oxycodone, morphine and fentanyl).

Comparison 1: hydromorphone compared with placebo

We identified no studies comparing hydromorphone with placebo.

Comparison 2: hydromorphone compared with oxycodone

Participant-reported pain intensity

We found no clear evidence of a difference in pain intensity (measured using a visual analogue scale (VAS)) in people treated with hydromorphone compared with those treated with oxycodone, but the evidence is very uncertain (3 RCTs, 381 participants, very low-certainty evidence).

Participant-reported pain relief

We found no studies reporting participant-reported pain relief.

Specific adverse events

We found no clear evidence of a difference in nausea (RR 1.13 95% CI 0.74 to 1.73; 3 RCTs, 622 participants), vomiting (RR 1.18, 95% CI 0.72 to 1.94; 3 RCTs, 622 participants), dizziness (RR 0.91, 95% CI 0.58 to 1.44; 2 RCTs, 441 participants) and constipation (RR 0.92, 95% CI 0.72 to 1.19; 622 participants) (all very low-certainty evidence) in people treated with hydromorphone compared with those treated with oxycodone, but the evidence is very uncertain.

Quality of life

We found no studies reporting quality of life.

Comparison 3: hydromorphone compared with morphine

Participant-reported pain intensity

We found no clear evidence of a difference in pain intensity (measured using the Brief Pain Inventory (BPI) or VAS)) in people treated with hydromorphone compared with those treated with morphine, but the evidence is very uncertain (2 RCTs, 433 participants; very low-certainty evidence).

Participant-reported pain relief

We found no clear evidence of a difference in the number of clinically improved participants, defined by 50% or greater pain relief rate, in the hydromorphone group compared with the morphine group, but the evidence is very uncertain (RR 0.99, 95% CI 0.84 to 1.18; 1 RCT, 233 participants; very low-certainty evidence).

Specific adverse events

At 24 days of treatment, morphine may reduce constipation compared with hydromorphone, but the evidence is very uncertain (RR 1.56, 95% CI 1.12 to 2.17; 1 RCT, 200 participants; very low-certainty evidence). We found no clear evidence of a difference in nausea (RR 0.94, 95% CI 0.66 to 1.30; 1 RCT, 200 participants), vomiting (RR 0.87, 95% CI 0.58 to 1.31; 1 RCT, 200 participants) and dizziness (RR 1.15, 95% CI 0.71 to 1.88; 1 RCT, 200 participants) (all very low-certainty evidence) in people treated with hydromorphone compared with those treated with morphine, but the evidence is very uncertain.

Quality of life

We found no studies reporting quality of life.

Comparison 4: hydromorphone compared with fentanyl

Participant-reported pain intensity

We found no clear evidence of a difference in pain intensity (measured by numerical rating scale (NRS)) at 60 minutes in people treated with hydromorphone compared with those treated with fentanyl, but the evidence is very uncertain (1 RCT, 82 participants; very low-certainty evidence).

Participant-reported pain relief

We found no studies reporting participant-reported pain relief.

Specific adverse events

We found no studies reporting specific adverse events.

Quality of life

We found no studies reporting quality of life.

Authors' conclusions

The evidence of the benefits and harms of hydromorphone compared with other analgesics is very uncertain. The studies reported some adverse events, such as nausea, vomiting, dizziness and constipation, but generally there was no clear evidence of a difference between hydromorphone and morphine, oxycodone or fentanyl for this outcome.

There is insufficient evidence to support or refute the use of hydromorphone for cancer pain in comparison with other analgesics on the reported outcomes. Further research with larger sample sizes and more comprehensive outcome data collection is required.

PLAIN LANGUAGE SUMMARY

Hydromorphone for the treatment of cancer pain

Background

Over 75% of people with cancer experience pain. Around 30% to 50% of these people have moderate to severe pain, which can have a negative impact on daily life. Cancer pain is a distressing symptom that tends to worsen as the disease progresses. Hydromorphone may help relieve these symptoms. Cancer-related pain is usually treated with medicines such as morphine, oxycodone, fentanyl or hydromorphone. This review looked at the benefits and harms of hydromorphone compared with other medicines.

Study characteristics

In November 2020, we updated our searches for randomised controlled studies of hydromorphone compared with placebo, an alternative opioid or another active control. Randomised controlled studies are studies where people are randomly placed into different treatment groups. We found four studies that compared hydromorphone with oxycodone, three studies that compared hydromorphone with morphine and one study that compared hydromorphone with fentanyl.

Results

This review includes eight studies (four new studies included in this updated version) with 1283 participants comparing hydromorphone with oxycodone, morphine or fentanyl in adults (aged 18 years and above) with moderate to severe cancer pain. None of the studies compared hydromorphone and placebo. None of the studies included children.

We found no differences in pain intensity scores between the different treatment groups and on average patients reported low levels of pain after opioid administration. Hydromorphone seemed to work as well as morphine, oxycodone and fentanyl. There were some side effects, such as nausea, vomiting, dizziness and constipation, but generally there was no clear difference between people taking hydromorphone and people taking morphine, oxycodone or fentanyl.

Certainty of the evidence

We rated the certainty of the evidence from studies using four levels: very low, low, moderate or high. Very low-certainty evidence means that we are very uncertain about the results. High-certainty evidence means that we are very confident in the results. No results were rated as high certainty; we only identified very low-certainty evidence for pain intensity, pain relief and side effects. These outcomes were rated as very low certainty because there were either few trials included with few participants, or due to other sources of bias, such as potential competing interests with the pharmaceutical industry.

Conclusions

The studies did not provide enough high-certainty evidence to draw firm conclusions; the evidence of the benefits and harms of hydromorphone compared with other medicines is very uncertain.

Summary of findings 1. Hydromorphone compared with oxycodone for people with moderate to severe cancer pain

Hydromorphone compared with oxycodone for people with moderate to severe cancer pain

Patient or population: people with moderate to severe cancer pain

Setting: unclear, not specified in included studies

Intervention: hydromorphone

Comparison: oxycodone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with oxycodone	Risk with hydromorphone				
Participant-reported pain intensity (as measured by VAS or BPI) Follow-up: 5–28 days	For pain intensity, the results were similar in hydromorphone and oxycodone groups, although data were skewed. Only 1 study showed mean pain levels of 'no worse than mild pain' for oxycodone and hydromorphone groups.		—	462 (4 RCTs)	⊕⊖⊖⊖ **Very low** a,b,c	Pain intensity scores: 3 studies (n = 381) using VAS (0–100, higher = worse outcome): mean endpoint score for hydromorphone in each study was 28.86 (SD 17.08, n = 19); 23 (SD 17.91, n = 86); 24.7 (SD 22.1, n = 88). Mean endpoint score for oxycodone in each study was 30.30 (SD 25.33, n = 12); 23.2 (SD 18.83, n = 92); 27.9 (SD 21.05, n = 84). 1 study using BPI (0–10; higher = worse outcome): mean change score of 'pain at its worst in the past 24 hours' for hydromorphone −1.8 (SD 3.29, n = 81).
Participant-reported pain relief	Not reported.					
Specific adverse events – nausea Follow-up: 5–28 days	**Study population**		**RR 1.13** (0.74 to 1.73)	622 (3 RCTs)	⊕⊖⊖⊖ **Very low** a,b,c,d	—
	288 per 1000	326 per 1000 (213 to 499) more				
	Moderate					

	237 per 1000	267 per 1000 (175 to 409)				
Specific adverse events – vomiting Follow-up: 5–28 days	**Study population**		**RR 1.18** (0.72 to 1.94)	622 (3 RCTs)	⊕⊖⊖⊖ **Very low** a,b,c,d	—
	282 per 1000	333 per 1000 (203 to 547) more				
	Moderate					
	225 per 1000	265 per 1000 (162 to 436)				
Specific adverse events – dizziness Follow-up: 7–28 days	**Study population**		**RR 0.91** (0.58 to 1.44)	441 (2 RCTs)	⊕⊖⊖⊖ **Very low** a,b,c	—
	143 per 1000	131 per 1000 (83 to 207) fewer				
	Moderate					
	132 per 1000	120 per 1000 (77 to 191)				
Specific adverse events – constipation Follow-up: 5–28 days	**Study population**		**RR 0.92** (0.72 to 1.19)	622 (3 RCTs)	⊕⊖⊖⊖ **Very low** a,b,c	—
	282 per 1000	259 per 1000 (203 to 336) fewer				
	Moderate					
	270 per 1000	248 per 1000 (194 to 321)				
Quality of life	Not reported.					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

BPI: Brief Pain Inventory; **CI:** confidence interval; **n:** number of participants; **RCT:** randomised controlled trial; **RR:** risk ratio; **SD:** standard deviation; **VAS:** visual analogue scale.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded twice due to very serious study limitations: studies were rated at high risk of bias overall, mainly accounted for by attrition bias and funding bias.
[b]Downgraded once due to serious imprecision: all studies had fewer than 200 participants in each treatment arm. Also sample size was smaller than optimal information size (GRADE guidelines 6, Guyatt 2011); CIs around estimate of effect were wide and included null effect and appreciable benefit/harm.
[c]Decision taken not to downgrade due to publication bias: although publication bias was highly suspected due to the small number of trials identified, this outcome had already been downgraded three times for other factors, therefore, further downgrading would be inappropriate.
[d]Decision taken not to downgrade due to inconsistency: although inconsistency was highly suspected due to I^2 value greater than 50% with unexplainable heterogeneity, this outcome had already been downgraded three times for other factors, therefore, further downgrading would be inappropriate.

Summary of findings 2. Hydromorphone compared with morphine for people with moderate to severe cancer pain

Hydromorphone compared with morphine for people with moderate to severe cancer pain

Patient or population: people with moderate to severe cancer pain

Setting: inpatients, outpatients and day patients

Intervention: hydromorphone

Comparison: morphine

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with morphine	Risk with hydromorphone				
Participant-reported pain intensity (as measured by BPI and VAS) Follow-up: 12 weeks	For pain intensity measured by BPI at 24 days, the results showed slightly higher mean endpoint scores for 'worst pain' in morphine group and similar mean scores for 'average' and 'least' pain in hydromorphone and morphine groups. For pain intensity measured by VAS from weeks 1–12, both morphine and hydromorphone groups had mean pain levels of 'no worse than mild pain.' Evidence of hydromorphone vs morphine on pain intensity was very uncertain.		—	433 (2 RCTs)	⊕⊖⊖⊖ **Very low** [a,b,c]	1 study (n = 200) using subscale data derived from BPI scale (0–10; higher = worse outcome): mean endpoint score for 'worst pain:' hydromorphone 3.5 (SD 2.9, n = 99); morphine 4.3 (SD 3.0, n = 101). Mean scores on 'least pain' and 'average pain' were almost identical. 1 study (n = 233) using VAS scale (0–10; higher = worse outcome) measured pain intensity from week 1 to week 12 of treatment. Both groups had identical scores at all the measured timepoints (P > 0.05).
Participant-reported pain relief	**Study population**		**RR 0.99** (0.84 to 1.18)	233 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,b,c]	—

Follow-up: mean 12 weeks	705 per 1000	698 per 1000 (593 to 832)				
Specific adverse events – nausea Follow-up: 24 days	**Study population**		**RR 0.94** (0.66 to 1.30)	200 (1 RCT)	⊕⊖⊖⊖ **Very low** a,b,c	—
	396 per 1000	372 per 1000 (261 to 515) fewer				
Specific adverse events – vomiting Follow-up: 24 days	**Study population**		**RR 0.87** (0.58 to 1.31)	200 (1 RCT)	⊕⊖⊖⊖ **Very low** a,b,c	—
	337 per 1000	293 per 1000 (195 to 441) fewer				
Specific adverse events – dizziness Follow-up: 24 days	**Study population**		**RR 1.15** (0.71 to 1.88)	200 (1 RCT)	⊕⊖⊖⊖ **Very low** a,b,c	—
	228 per 1000	262 per 1000 (162 to 428) more				
Specific adverse events – constipation Follow-up: 24 days to 12 weeks	The higher incidence of constipation of hydromorphone occurred at a shorter treatment point (at 24 days of treatment), but not a longer treatment point (12 weeks).		—	433 (2 RCTs)	⊕⊖⊖⊖ **Very low** a,b,c	2 studies reported the incidence of constipation at different timepoints. 1 study (n = 200) measured at 24 days of treatment found a significantly higher incidence of constipation with hydromorphone than with morphine (RR 1.56, 95% CI 1.12 to 2.17; P = 0.009). 1 study (n = 233) measured at 12 weeks' follow-up found no clear difference between 2 groups (RR 0.65, 95% CI 0.42 to 1.00; P = 0.055).
Quality of life	Not reported.					

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

BPI: Brief Pain Inventory; **CI:** confidence interval; **n:** number of participants; **RCT:** randomised controlled trial; **RR:** risk ratio; **SD:** standard deviation; **VAS:** visual analogue scale.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded twice due to very serious study limitations: all studies were rated at high risk of bias for at least two domains.
[b]Downgraded once due to serious imprecision: studies contained fewer than 200 participants in each treatment arm, and sample size was smaller than optimal information size (Guyatt 2011); CI around estimate of effect was wide and included no effect and appreciable benefit/harm.
[c]Decision made not to downgrade due to publication bias: although publication bias was highly suspected due to the small number of trials identified, this outcome had already been downgraded three times for other factors, therefore, further downgrading would be inappropriate.

Summary of findings 3. Hydromorphone compared with fentanyl for people with moderate to severe cancer pain

Hydromorphone compared with fentanyl for people with moderate to severe cancer pain

Patient or population: people with moderate to severe cancer pain

Setting: included studies did not specify inpatients, outpatients or community settings

Intervention: hydromorphone

Comparison: fentanyl

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
Participant-reported pain intensity (as measured by NRS) Follow-up: mean 1 day	1 study (n = 82) measured pain intensity using NRS at 60 minutes after treatment initiation. The mean decrease from pain score at randomisation showed no clear difference between the 2 groups (MD −0.24, 95% CI −1.21 to 0.73; P = 0.63). In addition, the mean decrease from maximum pain score of 10 for the hydromorphone group and from randomisation pain score for the fentanyl group showed no clear difference (MD 0.81, 95% CI −0.18 to 1.80; P = 0.11).	82 (1 RCT)	⊕⊖⊖⊖ **Very low** [a,b,c]
Participant-reported pain relief	Not reported.		
Specific adverse events – nausea	Not reported.		
Specific adverse events – vomiting	Not reported.		
Specific adverse events – dizziness	Not reported.		
Specific adverse events – constipation	Not reported.		
Quality of life	Not reported.		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **n:** number of participants; **MD:** mean difference; **NRS:** numerical rating scale; **RCT:** randomised controlled trial.

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgraded twice due to very serious study limitations: study was rated at high risk of bias for at least two domains.
[b]Downgraded once due to serious imprecision: CIs around estimate of effect were wide and included null effect and appreciable benefit/harm.
[c]Decision made not to downgrade due to publication bias: although publication bias was highly suspected due to the small number of trials identified, this outcome had already been downgraded three times by other factors, therefore further downgrade would be inappropriate.

BACKGROUND

This is an update of a previously published review in the Cochrane Library entitled 'Hydromorphone for cancer pain' (Bao 2016). The previous review updated and replaced the published 'Hydromorphone for acute and chronic pain' review, which was withdrawn because the original author team were unavailable to update it (Quigley 2013). The scope of the current review is limited to cancer pain.

Description of the condition

Pain is defined as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" (IASP 2020). Cancer-related pain can be classified as acute or chronic, though it is sometimes thought to be an ongoing acute pain. Acute pain is defined as having "a temporal pattern of onset … generally associated with subjective and objective physical signs" (Meier 2010), whereas chronic pain is more continuous, and lasts or recurs for more than three months (ICD-11 2019). Although pain is not necessarily inevitable for people who are diagnosed with cancer, it is an important and distressing common symptom of the disease, which tends to increase in frequency and intensity as the cancer advances. One previous systematic review indicated the prevalence of pain to be more than 50% in all cancer types (Van den Beuken-van Everdingen 2007). For people with advanced cancer, the prevalence of pain can be as high as 90% (Laird 2008). One more recent systematic review reported a prevalence rate of 66.4% in advanced, metastatic or terminal disease; 40% after curative treatment; and 55% during anticancer treatment, which indicates that the prevalence of cancer pain remains high (Van den Beuken-Van MH 2016).

Epidemiological studies suggest that approximately 15% of people with cancer who experience pain fail to achieve acceptable pain relief with conventional management (Running 2011; Yakovlev 2008). It has been estimated that 30% to 50% of people with cancer categorise their pain as moderate to severe and that between 75% and 90% of people with cancer experience pain which has a major impact on their daily life (Portenoy 1999). Uncontrolled pain can lead to physical and psychological distress (Van den Beuken-Van MH 2016), and can have a drastic effect on people's quality of life (Green 2011).

Description of the intervention

The use of interventions for managing cancer pain, including pharmacological treatments (e.g. opioid analgesics), psychological therapy (e.g. cognitive behavioural therapy) and alternative treatments (e.g. acupuncture or massage), commonly rely on recommendations given by clinical practice guidelines.

The European Society for Medical Oncology (ESMO) Clinical Practice Guidelines gives recommendations for adults according to the severity of cancer pain (ESMO 2018) based on data from the World Health Organization (WHO) recommendations (WHO 1986). For treatment of mild pain, paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) are recommended; for treatment of mild to moderate pain, weak opioids (e.g. tramadol, dihydrocodeine and codeine) are recommended with a combination of non-opioid analgesics; for treatment of moderate to severe pain, strong opioids are recommended, and the first choice is oral morphine (Hanks 2001). This recommendation is largely due to its cost and availability rather than proven superiority (Caraceni 2012), with a previous review suggesting that a clear proportion of people do not achieve sufficient pain relief by taking morphine due to unmanageable adverse events, including nausea, delirium or myoclonus (muscle spasm) (Murray 2005). However, evidence from one Cochrane Review on oral morphine for cancer pain suggested that only around 5% of participants stopped taking morphine due to lack of pain relief or unacceptable adverse events (Wiffen 2013). Morphine has also been associated with toxicity in people with renal impairment (King 2011a). In the National Comprehensive Cancer Network (NCCN) guidelines for adult cancer pain, the use of opioids is also recommended according to severity of pain; and the recommended dose of opioids is introduced in morphine sulphate or equivalent (NCCN 2021).

In 2019, the WHO updated the guideline for pharmacological and radiotherapeutic management of cancer pain in adults and adolescents. The new guideline recommends considering the use of non-opioids (e.g. paracetamol or NSAIDs) for the initiation of pain relief; for the maintenance of pain relief, any weak or strong opioid (e.g. codeine, morphine, methadone, hydromorphone, oxycodone or fentanyl) or a combination of opioids with NSAIDs should be considered depending on clinical assessment and pain severity (WHO 2019a). It is noteworthy that the latest WHO guideline states that the choice of opioid analgesic may make little or no difference in speed of pain relief, duration of maintenance of pain reduction or functional outcomes.

However, partially due to the recommendation of the use of opioids in the management of cancer pain in most international clinical guidelines, the prescriptions for opioids for pain relief increased (Han 2019). The side effect of opioid overdose can cause opioid dependence and other health problems (WHO 2019b). Although one report indicated that the opioid overdose mortality rate decreased in the US during 2017 to 2018, it is still a noteworthy issue since the rate of overdose mortality involving synthetic opioids, mainly accounted for by fentanyl, increased relatively (Wilson 2020).

Hydromorphone (also known as dihydromorphinone) is a semi-synthetic derivative of morphine and is marketed in various countries under a range of brand names. Since its clinical introduction in 1926, it has been used as an alternative opioid analgesic to morphine, as it has a similar chemical structure but is more lipid soluble (Urquhart 1988) and potent (Twycross 1994). Hydromorphone hydrochloride has high aqueous solubility and is beneficial for people who require higher doses (Portenoy 2011), and OROS (osmotic-controlled release oral delivery system) hydromorphone extended release (ER) is five times as potent as morphine, and has 8.5 times the equianalgesic effect when administered intravenously (Binsfeld 2010; Sarhill 2001). This also allows a smaller dose of hydromorphone to be used for an equianalgesic effect. Hydromorphone is administered through several routes (e.g. oral, intravenous, subcutaneous, epidural and intrathecal) (Murray 2005).

How the intervention might work

Like morphine, hydromorphone is primarily an agonist at μ-opioid receptors, displaying weak affinity for κ-opioid receptors. μ-Opioid receptors mediate pain-relieving properties but they can also result in adverse events such as nausea, constipation and respiratory depression (Murray 2005). One systematic review showed that

hydromorphone had similar analgesic and adverse effects to morphine (Miller 1999), while recent reviews concluded that no study has yet clearly demonstrated whether hydromorphone is better than oral morphine (Pigni 2011; Schuster 2018).

Hydromorphone, in common with other opioid analgesics, has the potential to produce adverse events that include respiratory depression, nausea, vomiting, constipation and itching. Tolerance may develop during chronic opioid therapy such that larger doses may be required to sustain the analgesic effect. In addition, people can be at risk of physiological dependence and experience opioid withdrawal syndrome upon sudden cessation of the opioid or administration of an antagonist. When used for the relief of pain in malignant disease, the actions of relieving anxiety, producing drowsiness and allowing sleep may be welcome (Grahame-Smith 2002).

Why it is important to do this review

This is one of a suite of Cochrane Reviews investigating analgesics for cancer pain in adults (Derry 2017; Hardy 2015; Wiffen 2013; Wiffen 2017a; Wiffen 2017b). Although the WHO recommends oral morphine as a first-line analgesia for cancer-related pain, the use of hydromorphone remains a consideration in some circumstances (Wiffen 2013). Previous systematic reviews have compared the efficacy and adverse effects of hydromorphone with other medications, but the inconsistency of their conclusions and the limited (low to moderate) methodological quality of the studies that were included suggested that further research is needed (Pigni 2011).

Our previous review in 2016 included four trials with limited data and indicated little difference between hydromorphone and other opioids, including morphine and oxycodone, in terms of analgesic efficacy and safety. The overall quality of evidence was relatively very low due to risk of bias, imprecision of effect estimates and publication bias.

During the previous four years, more trials might have been conducted to help determine the effectiveness and safety of different opioids due to the changes made to the definition of pain and the new updated international clinical guidelines. This new evidence may change the estimates of effect. Therefore, we aimed to update the review by searching for evidence between 2016 and 2020 in order to provide an up-to-date and more comprehensive result.

OBJECTIVES

To determine the analgesic efficacy of hydromorphone in relieving cancer pain, as well as the incidence and severity of any adverse events.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs) are the best design to minimise bias when evaluating the effectiveness of an intervention. We included RCTs that focused on hydromorphone for the treatment of cancer pain and assessed pain as an outcome measure in this review. The RCTs included parallel or cross-over studies of any duration. We excluded studies that did not state that participants were allocated at random.

Types of participants

We intended to include studies of adults and children with moderate to severe cancer pain (as defined in each study) who were clinically assessed as requiring treatment with opioid analgesia.

One of the reasons for including adults and children with moderate to severe cancer pain is that these people may experience increased and stronger negative impacts such as poorer sleeping quality, depression and emotional impacts, whereas people with mild pain are more likely to tolerate these negative impacts. In addition, hydromorphone is categorised as a strong opioid, which is stated clearly in international guidelines that is recommended to manage moderate to severe pain.

Types of interventions

We included studies in which hydromorphone (any dose and route of administration) was the active intervention. Comparison treatments included placebo, an alternative opioid or another active control.

Types of outcome measures

We assessed participant-reported pain intensity and pain relief using any validated pain scales (e.g. visual analogue scale (VAS) and categorical scales), at any timepoint.

Primary outcomes

- Participant-reported pain intensity levels measured using a validated VAS or categorical pain scale. We were particularly interested in, but not limited to, numbers of participants who achieved 'no worse than mild pain' (Moore 2013). "No or mild pain" has been previously considered as: 3/10 on a numerical rating scale, or 30/100 mm on a VAS (Wiffen 2013). We did not consider physician, nurse or carer-reported measures of pain.
- Participant-reported pain relief measured using a validated scale.

Secondary outcomes

- Specific adverse events, for example, drowsiness/sedation, nausea, vomiting, dizziness, constipation (incidence and severity, as defined and measured in each study).
- Serious adverse events (SAE), as defined and reported in each study.
- Improvement in participants' quality of life measured using the EuroQol EQ-5D, the WHO Quality of Life Assessment or a similar validated quality of life instrument.
- Leaving the study early or discontinuation of treatment for any reason.
- Death.

Search methods for identification of studies

Electronic searches

For this update, we searched the following databases to identify potentially relevant studies to be assessed for inclusion in this review. See Appendix 1 for previous search strategies. See Appendix 2 for update search strategies from April 2016 to 23 November 2020.

- Cochrane Central Register of Controlled Trials (CENTRAL), CRSO, April 2016 to November 2020.
- MEDLINE (Ovid) April 2016 to 23 November 2020.
- Embase (Ovid) April 2016 to 23 November 2020.

Searching other resources

We manually checked the references of each included paper in an attempt to identify any relevant published or unpublished reports not found in the electronic searches. We contacted the authors of each included paper and of publications that were only available in abstract format. Where possible, we contacted representatives from the pharmaceutical companies marketing hydromorphone to ask for any relevant published or unpublished studies or missing data.

There were no limitations on publication date or language. We planned to translate any non-English papers had this been necessary. We also searched for ongoing trials in ClinicalTrials.gov (www.clinicaltrials.gov) and the WHO registry (International Clinical Trials Registry Platform; ICTRP) (www.who.int/ictrp/en/).

Data collection and analysis

Selection of studies

Two review authors (YL and YLiq) assessed the titles and abstracts of all studies identified by the searches and independently considered the full records of all potentially relevant studies for inclusion by applying the selection criteria outlined in the Criteria for considering studies for this review section. We resolved disagreements by discussion. We did not restrict the inclusion criteria by date or language. To promote transparency of the search and systematic review process, we produced a PRISMA flow diagram (Figure 1), as per the PRISMA statement (Moher 2009).

Figure 1. Study flow diagram (update).

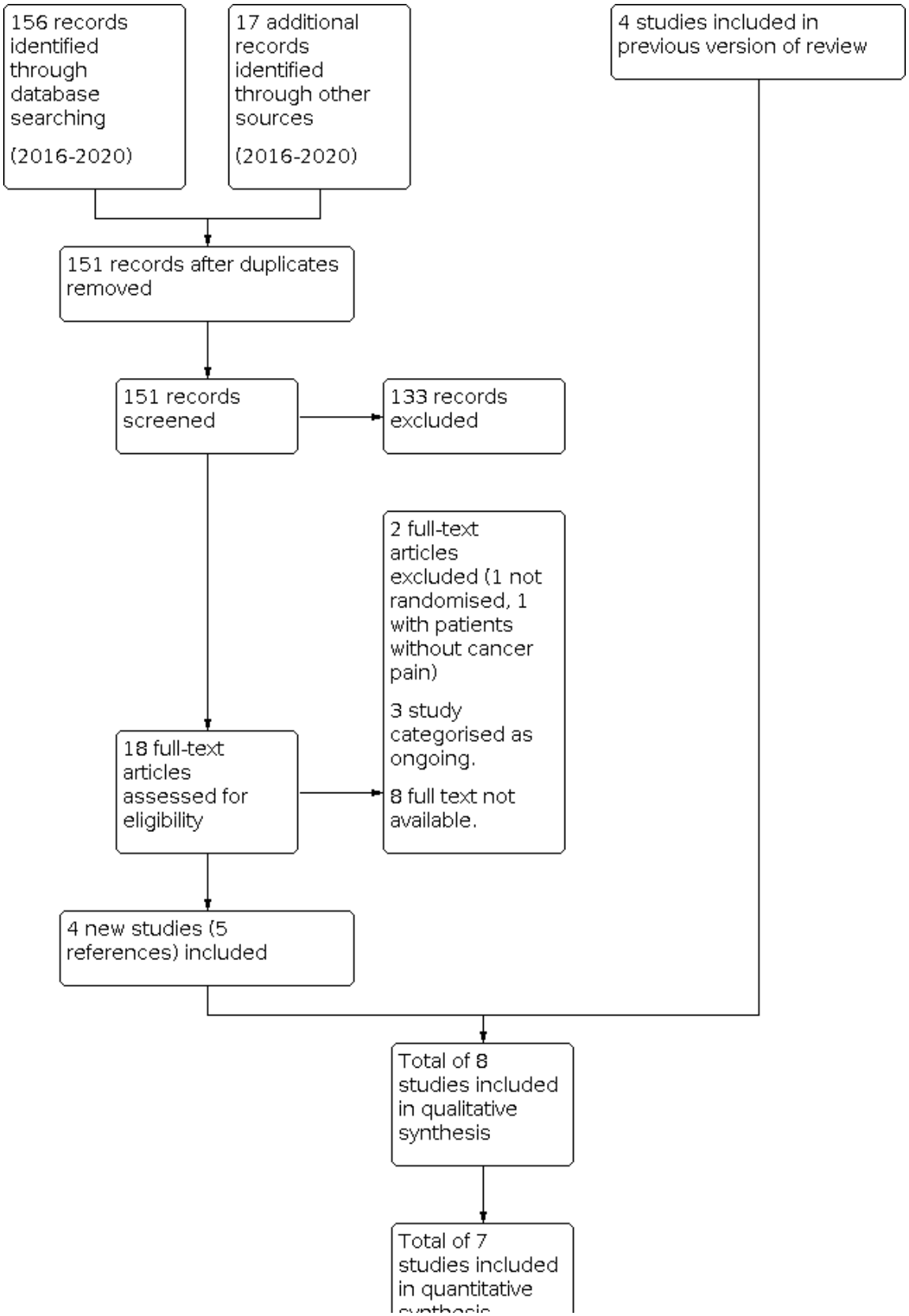
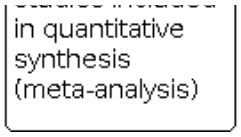


Figure 1. (Continued)



Data extraction and management

We extracted data using the Cochrane Pain, Palliative and Supportive Care Group's recommended data extraction form and recorded baseline data on participants, details of interventions, outcomes and results relevant to our review. Had we identified any studies that included a subset of participants who received hydromorphone, we planned to extract data for this group. We resolved any disputes by discussion.

Assessment of risk of bias in included studies

Two review authors (ZD and GL) independently assessed the methodological quality of each included study using the risk of bias assessment method outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019), with any disagreements resolved by discussion. We completed a risk of bias table for each included study using the risk of bias tool in Review Manager 5 (Review Manager 2014).

We assessed the following domains for each study.

- Random sequence generation (checking for possible selection bias). We assessed the method used to generate the allocation sequence as: low risk of bias (any truly random process, e.g. random number table; computer random number generator) or unclear risk of bias (method used to generate sequence not clearly stated). We excluded studies using a non-random process (e.g. odd or even date of birth; hospital or clinic record number).
- Allocation concealment (checking for possible selection bias). The method used to conceal allocation to interventions prior to assignment determines whether intervention allocation could have been foreseen in advance of, or during, recruitment, or changed after assignment. We assessed the methods as: low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes) or unclear risk of bias (method not clearly stated). We excluded studies that did not conceal allocation (e.g. open list).
- Blinding of participants and personnel (checking for possible performance bias). We assessed the methods used to blind study participants and personnel from knowledge of which intervention a participant received. We assessed methods as: low risk of bias (study stated that it was blinded and described the method used to achieve blinding, such as identical tablets matched in appearance or smell, or a double-dummy technique) or unclear risk of bias (study stated that it was blinded but did not provide an adequate description of how it was achieved). We considered studies that were not double-blind to have high risk of bias.
- Blinding of outcome assessment (checking for possible detection bias). We assessed the methods used to blind study participants and outcome assessors from knowledge of which intervention a participant received. We assessed the methods as: low risk of bias (study had a clear statement that outcome assessors were unaware of treatment allocation, and ideally described how this was achieved); unclear risk of bias (study states that outcome assessors were blind to treatment allocation but lacked a clear statement on how it was achieved). We considered studies where outcome assessment was not blinded as having a high risk of bias.
- Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data). We assessed the methods used to deal with incomplete data as: low risk (less than 10% of participants did not complete the study or used 'baseline observation carried forward' analysis (BOCF), or both); unclear risk of bias (used 'last observation carried forward' analysis) or high risk of bias (used 'completer' analysis).
- Selective reporting (checking for reporting bias). We assessed whether primary and secondary outcome measures were prespecified and whether these were consistent with those reported: we assessed as low risk those studies that prespecified outcomes (e.g. in a published protocol), unclear risk to those studies that provided no information on this domain and high risk to studies that had evident inconsistencies between outcomes (e.g. between protocol and the trial publication).
- Other sources of bias, for example funding sources for the studies (checking for possible conflicts of interest raised by the funding). We assessed studies as being at low risk of bias (no notable concerns, e.g. funding by governmental institution), high risk of bias (notable concerns, e.g. funding by pharmaceutical company) or unclear risk of bias (funding source not disclosed).

We assessed overall risk of bias according to the Cochrane Handbook (Higgins 2019).

Measures of treatment effect

We calculated the risk ratio (RR) and the corresponding 95% confidence intervals (CI) and P value for dichotomous outcomes. We calculated the mean difference (MD) and its corresponding 95% CI when means and standard deviations (SD) were available for continuous outcomes. If such information was unavailable, we planned to use the methods described in Chapter 16 of the *Cochrane Handbook for Systematic Reviews of Interventions* to calculate standardised mean differences (SMD) from, for example, F ratios, t values, Chi^2 values and correlation coefficients (Higgins 2019). In cases where continuous measures were used to assess the same outcomes using different scales, we planned to pool these data using Hedges' g to estimate the SMD if such information was unavailable. We planned to report study-level effects narratively when effect sizes could not be pooled. We would also have calculated numbers needed to treat for an additional beneficial outcome (NNTB) and additional harmful outcomes (NNTH).

We narratively described the data for continuous outcomes that were skewed. We defined skewed data according to Section 10.5.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019).

Unit of analysis issues

We only included studies that randomised the individual participant. For cross-over trials, one major concern is carry-over effect, which occurs when an effect of the treatment in the first phase is carried over to the second phase. We only used data from the first phase of cross-over studies to avoid the carry-over effect.

Dealing with missing data

We assessed missing data in the included studies. Where possible, we investigated and reported the reasons and numbers of those dropping out of each included study. Where studies had missing data, we initially attempted to contact the study authors to obtain this information. We performed an ITT analysis for dichotomous outcomes. If there was missing participant information, we recorded this and commented in the individual study's risk of bias table. We assigned participants with missing data to a 'zero improvement' category, and we performed a sensitivity analysis comparing the resulting effect sizes with those obtained using completer-only data. We intended to use BOCF, where rating scales were employed for continuous outcomes. However, this was not done as data of the few continuous outcomes were skewed.

Assessment of heterogeneity

We intended to assess for heterogeneity among primary outcome studies using the I^2 statistic along with its corresponding P and Chi^2 values (Higgins 2019), and discuss any observed heterogeneity and its magnitude. We used a P value of 0.10 to determine statistical significance of heterogeneity according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). We planned to investigate possible sources using subgroup analyses and sensitivity analyses had we identified important heterogeneity (I^2 greater than 50%).

Assessment of reporting biases

We searched for the original trial protocols of the included studies and compared the results with these when were possible. We compared the reported outcomes against the methods section of the paper to look for selective reporting of outcomes when no protocol was available.

Data synthesis

We entered all extracted data into Review Manager 5 software for analysis (Review Manager 2014). In order to take into account differences between studies, we synthesised data using a random-effects model. We used a fixed-effect model in a sensitivity analysis in order to investigate any differences in the estimate of effect. We meta-analysed the data where possible. Where this was not feasible, we summarised data narratively in the results and discussion sections and the relevant tables.

Subgroup analysis and investigation of heterogeneity

We planned to carry out the following subgroup analyses had there been data available:

- method of administration (long-acting versus short-acting);
- single dose versus multiple dose;
- type of cancer;
- age (adults versus children).

Sensitivity analysis

We planned to examine the robustness of meta-analyses by conducting the following sensitivity analysis had there been sufficient data available:

- exclude studies at 'high risk of bias' across any one of the risk of bias domains in order to assess any differences in the estimate of treatment effect;
- for high levels of attrition (greater than 10%) in individual studies, comparing completer-only data with our assumptions of ITT;
- to assess any differences when synthesising data using a fixed-effect rather than a random-effects model.

Summary of findings and assessment of the certainty of the evidence

Assessment of the certainty of the evidence

We assessed the overall certainty of the evidence for each outcome using GRADE (Guyatt 2011), and presented it in summary of findings tables to present the main findings of a review in a transparent and simple tabular format.

The GRADE system uses the following criteria for assigning grade of evidence.

- High: we are very confident that the true effect lies close to that of the estimate of the effect.
- Moderate: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- Low: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
- Very low: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

The GRADE system uses the following five domains to assess the certainty of evidence.

- Study limitations (risk of bias): refer to limitations in the study design, which would be assessed according to Cochrane risk of bias assessment (Higgins 2019).
- Inconsistency of results: refers to unexplained heterogeneity of results.
- Indirectness of evidence: refers to the uncertainty about directness.
- Imprecision: refers to uncertainty about the results.
- Publication bias: refers to a systematic underestimation or an overestimation of the underlying beneficial or harmful effect due to the selective publication of studies.

We downgraded the certainty of evidence if there was:

- risk of bias: serious (−1) or very serious (−2) limitation to study certainty;
- inconsistency: important unexplained heterogeneity (−1);
- indirectness: some (−1) or major (−2) uncertainty about directness;
- imprecision: imprecise or sparse data (−1);

- publication bias: high probability of reporting bias (−1).

Summary of findings table

We included three summary of findings tables, one comparing hydromorphone versus oxycodone, one comparing hydromorphone versus morphine and one comparing hydromorphone versus fentanyl. Had we identified any studies comparing hydromorphone versus placebo we planned to produce a summary of findings table for the comparison. We included key information concerning the certainty of evidence, the magnitude of effect of the interventions examined and the sum of available data on the outcomes:

- participant-reported pain intensity;
- participant-reported pain relief;
- specific adverse events: nausea, vomiting, dizziness, constipation
- quality of life.

RESULTS

Description of studies

Results of the search

Details of the search results are illustrated in the PRISMA table (Figure 1).

The searches of the three databases retrieved 156 records. Our screening of the reference lists of included publications revealed 17 additional records. There were 151 records after deduplication. We excluded 133 records based on titles and abstracts. We obtained the full text of the remaining 18 records. We excluded two studies (Amsbaugh 2016; Yang 2018) (see Characteristics of excluded studies table). We added eight records to the Characteristics of studies awaiting classification table due to the lack of access to full text (ACTRN12605000696695; ChiCTR-IPR-17013446; ChiCTR1900028015; ChiCTR2000037845; CTRI/2009/091/000244; EUCTR2004-005187-24-SK; EUCTR2008-002273-12-IT; JPRN-JapicCTI-142666). We identified three new ongoing studies (NCT02084355; NCT04243954; NCT04296305). We included four new studies (five references) in this update that were reported in four references (Banala 2020; Inoue 2017; Inoue 2018; Ma 2020). For a further description of our screening process, see the study flow diagram (Figure 1).

Included studies

We found eight RCTs including adults (1283 participants, with data for 1181 participants available for analysis) that satisfied the inclusion criteria of this review; four included in the previous version of the review (Hagen 1997; Hanna 2008; Moriarty 1999; Yu 2014), and four new studies (five references) for this update (Banala 2020; Inoue 2017; Inoue 2018; Ma 2020); see Characteristics of included studies table for a full description. We contacted the authors regarding the uncertainty of the uniqueness of Inoue 2017 and Inoue 2018, and received confirmation in their response that these were two separate studies. We found no studies that included children or studies that compared hydromorphone with placebo.

Design and setting

Six included studies were conducted in high-income countries. Hagen 1997 was conducted in Canada; Hanna 2008 was a multi-centre trial involving 37 centres in Belgium, Canada, France, Germany, the Netherlands, Spain, Sweden and the UK. This study reported that it included inpatients, outpatients and day patients. Moriarty 1999 was conducted in the UK. Inoue 2017 and Inoue 2018 were conducted in Japan. Banala 2020 was conducted in the US. The remaining two studies were conducted in China (Ma 2020; Yu 2014).

Two studies had a cross-over study design (Hagen 1997; Moriarty 1999), and four had a parallel study design (Banala 2020; Inoue 2017; Inoue 2018; Ma 2020). The other two had a two-stage, parallel design that included an initial titration stage followed by a slow release (SR) or maintenance phase (Hanna 2008; Yu 2014).

Sample sizes

Hagen 1997 was the smallest trial of the eight with 44 randomised participants, but only 31 people completed the trial. Hanna 2008 had a sample size of 200. Moriarty 1999 randomised 100 participants, but only 89 completed the trial. Yu 2014 randomised 260 participants, but only 137 completed the trial through to the end of maintenance phase. Inoue 2017 randomised 181 participants but only 147 completed the trial. Inoue 2018 also randomised 181 participants, but only 160 completed the trial. Banala 2020 randomised 84 participants and 82 completed the trial. Ma 2020 randomised 233 participants, and all the participants received the intervention as assigned. However, 211 participants dropped out due to various reasons during the three-month follow-up.

Participants

All eight studies included adults with cancer pain. The mean age in Hagen 1997, Hanna 2008, and Yu 2014 was 53 to 59 years with evenly distributed gender; Moriarty 1999 included people over 18 years but no age range was given. Inoue 2017 and Inoue 2018 required participants to be aged over 20 years, but no age range was given. The proportion of men in the studies ranged from 42% (Hagen 1997) to 67.4% (Inoue 2018). Banala 2020 included participants who were 22 to 84 years old, and Ma 2020 included participants who were 18 to 80 years old. Both studies included participants with evenly distributed gender. We found no studies including children. None of the studies stated the cancer stage.

The severity of cancer pain was unclear in Hagen 1997, but participants were on a stable dose of analgesics (active controlled-release). Participants in Hanna 2008 had moderate to severe pain and required 60 mg to 540 mg of oral morphine every 24 hours at baseline. Moriarty 1999 and Yu 2014 involved people with moderate to severe cancer pain. The locations of the primary tumour were mainly breast, colorectal, lung, prostate, gastrointestinal and central nervous system. A smaller proportion of participants had cancer in the oral cavity, lymphoma, leukaemia and bone cancer. Inoue 2017 and Inoue 2018 involved people with moderate to severe cancer pain. The locations of the primary tumour were mainly lung, gastrointestinal and hepatic-biliary pancreatic. A smaller proportion of participants had cancer of the urogenital system, head/neck and breast. Banala 2020 included people with severe cancer pain and who had been on opioid therapy for one

week or longer. Ma 2020 included people with moderate to severe cancer pain.

Interventions and comparators

Interventions included hydromorphone compared with oxycodone (Hagen 1997; Inoue 2017; Inoue 2018; Yu 2014), hydromorphone compared with morphine (Hanna 2008; Ma 2020; Moriarty 1999), and hydromorphone compared with fentanyl (Banala 2020).

Hydromorphone compared with oxycodone

Hagen 1997 compared controlled release (CR) hydromorphone versus CR oxycodone given every 12 hours for seven days. The mean daily doses were 24 (SD 4) mg for hydromorphone and 120 (SD 22) mg for oxycodone. Cross-over was completed without a washout period and we only used pre-crossover data.

Inoue 2017 compared ER hydromorphone versus ER oxycodone orally for seven days. The daily doses were 4 mg/day for hydromorphone and 10 mg/day for oxycodone.

Inoue 2018 compared hydromorphone tablet with oxycodone powder given four times a day for five days. The daily doses were 4 mg/day for hydromorphone and 10 mg/day for oxycodone.

In the two-stage Yu 2014 trial, the eight-day titration phase was followed by a 28-day maintenance phase. Both phases used CR formulations; OROS hydromorphone or oxycodone CR and the maximum daily doses were 32 mg for OROS hydromorphone and 80 mg for oxycodone CR.

Hydromorphone compared with morphine

The titration stage for Hanna 2008 used instant release (IR) formulations of either hydromorphone or morphine given every four hours (six times daily) for two to nine days. The titrated dosage of hydromorphone during this phase was 12 mg/day to 108 mg/day and for morphine was 62 mg/day to 540 mg/day. This was followed by a 10- to 15-day SR stage, when the same drugs were given but in a CR formulation; OROS hydromorphone once daily or morphine CR twice daily. The starting dose was the same level as dose-stable pain achieved in IR phase, adjusted as required every two days at most.

Ma 2020 used intrathecal hydromorphone with a mean starting daily infusion dose of 0.276 (SD 0.53) mg and intrathecal morphine with a mean starting daily infusion dose of 1.551 (SD 4.20) mg.

Moriarty 1999 used tablet formulation of hydromorphone CR 4 mg and morphine CR 30 mg.

Hydromorphone compared with fentanyl

Banala 2020 used intravenous hydromorphone 1.5 mg at time of initiation and allowed a rescue dose at time of 0.5 hour, and nasal spray fentanyl 100 µg at time of initiation and allowed a rescue dose at time of 0.5 hour.

Outcomes

We were able to collect data on participant-reported pain intensity, but the data were skewed. Other outcomes reported by the studies included adverse events, leaving the study early and death.

Funding sources

Pharmaceutical companies funded six included studies, including Purdue Pharma (Hagen 1997), Johnson & Johnson (Hanna 2008), Daiichi Sankyo co Ltd (Inoue 2017; Inoue 2018), Napp Laboratories Ltd (Moriarty 1999), and Assertio, Inc. (Banala 2020). One study reported their funding sources from a non-commercial organisation, the Science and Technology Commission of Shanghai Municipality (Ma 2020). One study did not report their funding sources (Yu 2014).

Excluded studies

We excluded six studies. Yang 2018 was an RCT and had relevant interventions, but included adults with acute postoperative pain after cancer surgery. The remaining five studies had relevant participants and interventions, but they were not RCTs (Amsbaugh 2016; Han 2014; Lee 2012; Wirz 2008; Wirz 2009). See Characteristics of excluded studies table for further details.

Studies awaiting classification

Eight studies are awaiting classification due to the lack of access to the full text (ACTRN12605000696695; ChiCTR-IPR-17013446; ChiCTR1900028015; ChiCTR2000037845; CTRI/2009/091/000244; EUCTR2004-005187-24-SK; EUCTR2008-002273-12-IT; JPRN-JapicCTI-142666). See Characteristics of studies awaiting classification table for further details.

Ongoing studies

We found four ongoing RCTs eligible for inclusion. One compared hydromorphone with placebo in adults with moderate to severe cancer pain with unclear total sample size and the status is recruiting (NCT04296305). One compared hydromorphone with oxycodone and fentanyl patch in adults with moderate to severe cancer pain with unclear total sample size and January 2016 as the expected completion date (NCT02084355). One compared intravenous hydromorphone with oral morphine in 95 adults with moderate to severe pain (NCT04243954). The study is completed but not published yet. We found no reports relating to this study in our latest searches. One compared fentanyl and other opioids (which includes hydromorphone and oxycodone), in adults with moderate to severe cancer pain, with 500 as the total expected sample size and January 2010 as the expected completion date (NCT00822614).

Risk of bias in included studies

See Figure 2 and Figure 3 for graphic representation of the risk of bias assessment.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

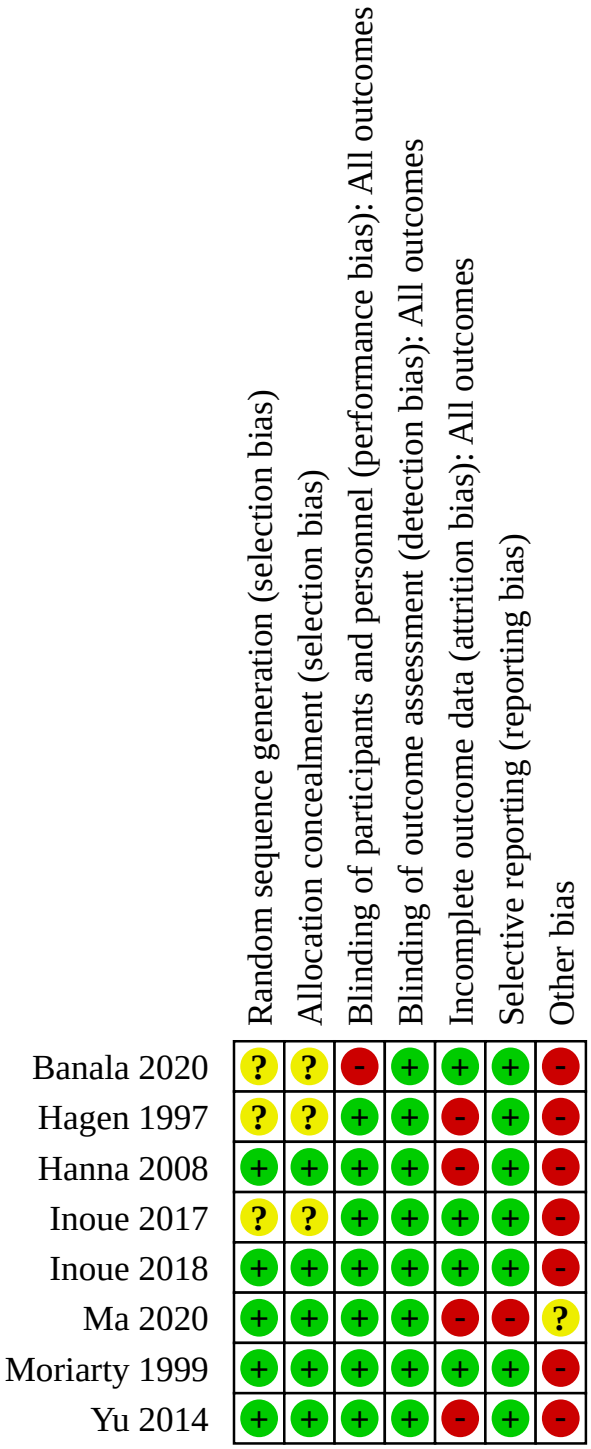
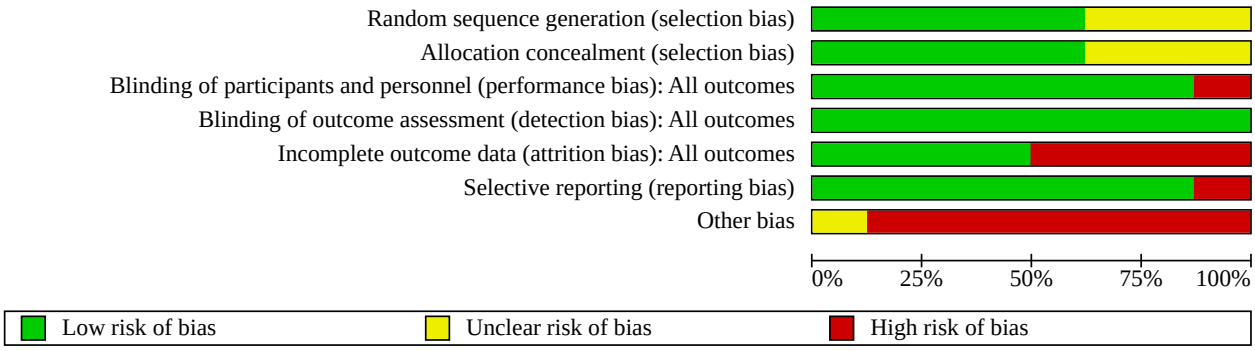


Figure 3. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.



Allocation

Random sequence generation

We assigned five studies at low risk of bias for random sequence generation (Hanna 2008; Inoue 2018; Ma 2020; Moriarty 1999; Yu 2014), and three at unclear risk of bias (Banala 2020; Hagen 1997; Inoue 2017).

Hanna 2008 and Inoue 2018 randomised participants on a 1:1 ratio via a central computer-generated randomisation list. Similarly, Yu 2014 used central randomisation (1:1) using an online dynamic minimisation allocation program. Moriarty 1999 employed a third-party randomisation method. Ma 2020 used a block random coding table for randomisation.

Hagen 1997, Inoue 2017, and Banala 2020 did not describe randomisation procedure in detail.

Allocation concealment

None of the studies provided explicit detail on allocation concealment. We considered Hanna 2008, Inoue 2018, and Ma 2020 as more likely to have used concealment since the randomisation was performed via a central list or block random coding table, and so we judged these studies at low risk of bias. We also judged Moriarty 1999 and Yu 2014 at low risk of bias because they used third-party randomisation, which typically conceals allocation.

We judged Banala 2020, Hagen 1997, and Inoue 2017 at unclear risk of bias because there were no details in the papers, thus we were unable to make any conclusive judgement.

Blinding

Blinding of participants and personnel

Six studies were described as double-blind, however Hanna 2008 did not provide further description of the blinding method; in this case, we accepted the author's reporting as true and accurate, and thus rated it at low risk of bias. Hagen 1997, Inoue 2017, Inoue 2018, and Moriarty 1999 used double-blind and double-dummy methods to protect the blinding. Yu 2014 did not offer an explicit description on blinding; however, we considered that double-blinding was likely to have been used, as the study employed over-encapsulated tablet and placebo to mask treatment, hence, we rated it at low risk of bias. Ma 2020 was reported as single blind with participants and investigators being blinded, hence, we rated it at low risk of bias. Banala 2020 was stated as an open-label design, hence, we rated it at high risk of bias.

Blinding of outcome assessment

It was unclear if the outcome assessment was blinded in any of the studies; however, as most of the outcomes were participant-reported, we rated this item at low risk of bias across all included studies.

Incomplete outcome data

Dropout was common and the proportion of dropout exceeded 10% in five studies (Hagen 1997; Hanna 2008; Ma 2020; Moriarty 1999; Yu 2014). Hanna 2008 had applied ITT analysis and the reasons and proportion for dropout was similar between groups, however, the dropout rate was greater than 10%, thus we rated it at high risk. We rated Hagen 1997 at high risk as it had over 10% dropout and these were excluded from final analysis, which further compromised the already weakened evidence. Sixty (46%) people dropped out of the hydromorphone group and 63 (48%) people dropped out of the oxycodone group in Yu 2014, but the proportion and reasons were balanced between groups. Nevertheless, we judged it at high risk because the dropout rate was greater than 10%. Ma 2020 reported that all participants received the intervention and 211 (90%) dropped out during the three-month follow-up period with reasons given and were included in the final analysis. Hence, we judged this study at high risk.

Moriarty 1999 had 11 (11%) participants drop out with reasons given and were included in the final analysis. The dropout rate was over 10%, but only marginally so. We considered the dropout was unlikely to have caused significant bias, as reasons and proportion of dropout were comparable between groups. Therefore, we judged this study at low risk of bias for this domain. The proportion of dropout was less than 10% in Banala 2020, Inoue 2017, and Inoue 2018, thus we judged them at low risk.

Selective reporting

Three trials had protocols, and we identified no differences between the planned outcome measures in the protocol and the reported outcome measures in the full report (Banala 2020; Hanna 2008; Yu 2014). Two trials had no available protocols, but when we compared the reported outcomes with the papers' methodology section we found no evidence of selective reporting (Hagen 1997;

Moriarty 1999). Therefore, we judged these five included studies at low risk of reporting bias. The other two trials also had no available protocols (Inoue 2017; Inoue 2018), but when we compared the reported outcomes with the papers' methodology sections we found both studies had non-reported planned outcomes. However, as the non-reported outcomes were not relevant to this review, we judged both studies at low risk of reporting bias.

Ma 2020 had a protocol and we identified that the predefined quality of life outcome was not reported in the published report, hence, we judged this study at high risk for this domain.

Other potential sources of bias

We judged seven studies at high risk of other bias as they were funded by pharmaceutical companies (Banala 2020; Hagen 1997; Hanna 2008; Moriarty 1999; Inoue 2017; Inoue 2018; Yu 2014). We judged Ma 2020 at unclear risk for this domain because the sponsorship of this study was not commercial (the Science and Technology Commission of Shanghai Municipality). However, the first author of this study was the person who reported grants, which may have led to a conflict of interest. Hence, we judged it at unclear risk for this domain.

Effects of interventions

See: **Summary of findings 1** Hydromorphone compared with oxycodone for people with moderate to severe cancer pain; **Summary of findings 2** Hydromorphone compared with morphine for people with moderate to severe cancer pain; **Summary of findings 3** Hydromorphone compared with fentanyl for people with moderate to severe cancer pain

We were able to extract numerical data from seven of the eight included studies (Banala 2020; Hagen 1997; Hanna 2008; Inoue 2017; Inoue 2018; Ma 2020; Yu 2014). Moriarty 1999 reported the outcomes with P values only.

Comparison 1: hydromorphone compared with placebo

We identified no studies comparing hydromorphone with placebo.

Comparison 2: hydromorphone compared with oxycodone

Four studies compared hydromorphone with oxycodone, including data from Hagen 1997 (n = 44), Inoue 2017 (n = 181), Inoue 2018 (n = 181), and Yu 2014 (n = 260).

2.1 Participant-reported pain intensity

Three studies reported participant-reported pain intensity using VAS scores (0 to 100 with a higher score indicating a worse outcome) (Hagen 1997; Inoue 2017; Inoue 2018). We presented data in separate tables because they were skewed.

In Hagen 1997, the mean VAS (high score = poor outcome) endpoint pain intensity scores at seven days of treatment were similar between groups (mean: hydromorphone 28.86 (SD 17.08), n = 19; oxycodone 30.30 (SD 25.33), n = 12; Analysis 1.1). Although according to the predefined threshold in the protocol (i.e. 30/100 mm on VAS), it was clear that the hydromorphone group achieved 'no worse than mild pain' and the oxycodone group did not achieve 'no worse than mild pain', the result needed careful interpretation because the data were skewed. Both groups achieved 'no worse than mild pain' on the categorical pain intensity as measured on an ordinal scale (higher = worse outcome) (mean: hydromorphone 1.5 (standard deviation (SD) 0.4) points; oxycodone 1.4 (SD 0.3) points; Table 1).

In Inoue 2017, the mean VAS endpoint pain intensity scores at seven days of treatment were similar between groups (mean: hydromorphone 23 (SD 17.91), n = 86; oxycodone 23.2 (SD 18.83), n = 92). The result reported by Inoue 2018 was consistent with Hagen 1997 and Inoue 2017 (hydromorphone 24.7 (SD 22.11), n = 88; oxycodone 27.9 (SD 21.05), n = 84).

Yu 2014 reported BPI score (0 to 10 with a higher score indicating a worse outcome). The BPI change score of 'pain at its worst in the past 24 hours' from baseline was similar between groups at 28 days of maintenance therapy (mean: hydromorphone −1.8 (SD 3.29), n = 40; oxycodone −1.7 (SD 3.91), n = 41; Table 1). The study reported only the mean BPI score for 'mean pain in the past 24 hours' (mean: hydromorphone 2.9; oxycodone 3.3, SDs not reported, n = 81).

None of the included studies reported number of participants who achieved 'no worse than mild pain'.

We rated the certainty of the evidence for participant-reported pain intensity as very low, downgrading twice for very serious study limitations and once for serious imprecision (Summary of findings 1). We decided not to downgrade for suspected publication bias as the outcome had already been downgraded three times for other factors, therefore, further downgrading would be inappropriate.

2.2 Participant-reported pain relief

No studies reported participant-reported pain relief.

2.3 Specific adverse events

Four studies reported specific adverse events (Hagen 1997; Inoue 2017; Inoue 2018; Yu 2014).

Hagen 1997 presented data using VAS at seven days of treatment in separate data tables because the continuous data for this outcome were skewed (Table 1). The mean endpoint nausea scores were comparable between groups (hydromorphone 16.05 (SD 17.51), n = 19; oxycodone 16.68 (SD 21.53), n = 12); there was no clear evidence of a difference (mean difference -4.89, 95% CI -22.15 to 12.37; Table 1).

The above findings were consistent with Yu 2014, Inoue 2017, and Inoue 2018, which indicated no clear evidence of a difference between groups at the end of treatment (ranged from five days of treatment to 28 days of maintenance therapy) for the following adverse events: nausea (RR 1.13, 95% CI 0.74, 1.73; n = 622); vomiting (RR 1.18, 95% CI 0.72 to 1.94; n = 622), dizziness (RR 0.91, 95% CI 0.58 to 1.44; n = 441) and constipation (RR 0.92, 95% CI 0.72 to 1.19; n = 622) (Analysis 1.2). There was no clear evidence of a difference between groups for other adverse events (Yu 2014). For single-study reported adverse events, see Table 2.

We rated the certainty of the evidence for specific adverse events as very low, downgrading the outcomes of nausea, vomiting, dizziness and constipation twice for very serious study limitations and once for serious imprecision. We decided not to downgrade for inconsistency and publication bias as the outcomes had already been downgraded three times for other factors, therefore, further downgrading would be inappropriate (Summary of findings 1).

2.4 Serious adverse events

Three studies involving 606 participants reported the incidence of serious adverse events (Inoue 2017; Inoue 2018; Yu 2014). We found no evidence of a difference between hydromorphone and oxycodone (RR 0.62, 95% CI 0.39 to 1.00; Analysis 1.3). We rated the certainty of the evidence as very low, downgrading twice for very serious study limitations and once for serious imprecision.

2.5 Quality of life

None of the studies reported quality of life.

2.6 Leaving the study early

Four studies involving 666 participants reported participants leaving the study early between five days to 28 days of maintenance (Hagen 1997; Inoue 2017; Inoue 2018; Yu 2014). We found no evidence of a difference between hydromorphone and oxycodone (RR 0.78, 95% CI 0.44 to 1.38; Analysis 1.4). We rated the certainty of the evidence as very low, downgrading twice for very serious study limitations (high risk of other bias and incomplete data) and imprecision.

2.7 Death

One study involving 260 participants reported death within 28 days of maintenance therapy (Yu 2014). This was claimed to be a consequence of disease progression, and there was no clear evidence of a difference between groups (RR 0.50, 95% CI 0.22 to 1.13; Table 2). Inoue 2017 reported deaths at five days of treatment and Inoue 2018 at seven days of treatment. However, they did not provide a specific number of deaths in each group. We rated the certainty of the evidence as very low, downgrading twice for very serious study limitations (high risk of other bias and incomplete data) and imprecision.

Sensitivity analysis for hydromorphone compared with oxycodone

We were unable to conduct any sensitivity analyses for individual studies comparing hydromorphone with oxycodone. All studies had a 'high risk of bias on any domain.' In addition, only Hagen 1997 and Yu 2014 reported larger dropout rates (greater than 10%). Because Hagen 1997 was not included in a meta-analysis, we performed a sensitivity analysis for adverse events reported by Yu 2014. When we included dropouts in the analysis, results were consistent with the original analysis, that there was no clear evidence of a difference between the two groups on adverse events outcomes.

Comparison 3: hydromorphone compared with morphine

Three studies reported data comparing hydromorphone with morphine (Hanna 2008; Ma 2020; Moriarty 1999).

3.1 Participant-reported pain intensity

Three studies reported participant-reported pain intensity (Hanna 2008; Ma 2020; Moriarty 1999).

Moriarty 1999 measured pain intensity (VAS) at three timepoints: before the morning dose, six hours after the morning dose and before the evening dose. The study reported that there was no clear evidence of a difference between groups at all time points (P = 0.68 before the morning dose, P = 0.90 six hours after the morning dose and P = 0.90 before the evening dose) (Moriarty 1999). It also reported that both treatments controlled pain satisfactorily (VAS from 8.47 mm to 10.43 mm), which indicated that participants in both groups achieved no worse than mild pain (less than 30 mm on the 0- to 100-mm VAS) (Moriarty 1999).

Hanna 2008 derived subscale data using the BPI scale measured at 24 days of treatment and found that the morphine group appeared to have a higher endpoint mean score on 'worst pain' (mean: hydromorphone 3.5 (SD 2.9), n = 99; morphine 4.3 (SD 3.0), n = 101; Table 3), nevertheless, mean scores on 'least pain' and 'mean pain' were almost identical. The 'mean pain' subscale data showed that both groups achieved no worse than mild pain.

Ma 2020 measured the categorical score on VAS from week one to week 12 of the treatment. The study reported that there was no clear evidence of a difference between groups at all time points (mean: week 1: hydromorphone 2.78 (SD 1.63), n = 121; morphine 2.56 (SD 1.20), n = 112; P = 0.245; week 2: hydromorphone 2.56 (SD 1.41), n = 121; morphine 2.58 (SD 1.21), n = 112; P = 0.908; week 3: hydromorphone 2.48 (SD 1.28), n = 121; morphine 2.62 (SD 1.24), n = 112; P = 0.388; week 4: hydromorphone 2.52 (SD 1.33), n = 121; morphine 2.56 (SD 1.10), n = 112; P = 0.794; week 5: hydromorphone 2.40 (SD 1.34), n = 121; morphine 2.63 (SD 1.13), n = 112; P = 0.165; week 6: hydromorphone 2.42 (SD 1.3), n = 121; morphine 2.57 (SD 1.22), n = 112); P = 0.350; week 7: hydromorphone 2.51 (SD 1.25), n = 121; morphine 2.53 (SD 1.07), n = 112; P = 0.881; week 8: hydromorphone 2.47 (SD 1.41), n = 121; morphine 2.40 (SD 1.00), n = 112; P = 0.692; week 9: hydromorphone 2.56 (SD 1.5), n = 121; morphine 2.54 (SD 1.11), n = 112; P = 0.909; week 10: hydromorphone 2.66 (SD 1.35), n = 121; morphine 2.52 (SD 1.06), n = 112; P = 0.382; week 11: hydromorphone 2.35 (SD 1.32), n = 121; morphine 2.39 (SD 1.06), n = 112); P = 0.815; week 12: hydromorphone 2.22 (SD 1.22), n = 121); morphine 2.37 (SD 1.03), n = 112; P = 0.344; Table 3).

We found no studies reporting the number of participants who achieved 'no worse than mild pain'.

We rated the certainty of the evidence for participant-reported pain intensity as very low, downgrading twice for very serious study limitations and once for serious imprecision (Summary of findings 2). We decided not to downgrade for publication bias as the outcome had already been downgraded three times for other factors, therefore, further downgrading would be inappropriate.

3.2 Participant-reported pain relief

Ma 2020 reported the number of participants with pain relief rate of 50% or greater at the end of the three-month follow-up period. There was no clear evidence of a difference between groups at the end of the follow-up period (RR 0.99, 95% CI 0.84 to 1.18; P = 0.962; Table 4).

We rated the certainty of the evidence for participant-reported pain relief as very low, downgrading twice for very serious study limitations and once for serious imprecision (Summary of findings 2). We decided not to downgrade for publication bias as the outcome had already been downgraded three times for other factors, therefore, further downgrading would be inappropriate.

3.3 Specific adverse events

Three studies reported specific adverse events (Hanna 2008; Ma 2020; Moriarty 1999).

Data from Hanna 2008 (measured within 24 days of treatment) showed that there was no evidence of a difference between groups for nausea, vomiting and dizziness. Constipation was less frequent with morphine compared with hydromorphone (Table 4).

- Nausea (RR 0.94, 95% CI 0.66, 1.30; n = 200).
- Vomiting (RR 0.87, 95% CI 0.58, 1.31; n = 200).
- Dizziness (RR 1.15, 95% CI 0.71, 1.88; n = 200).
- Constipation (RR 1.56, 95% CI 1.12 to 2.17; n = 200).

There were lower risks of confusion and diarrhoea in the morphine group once we had taken into account the missing data in a sensitivity analysis (see Table 4) (Hanna 2008). However, for data based on completers only (Hanna 2008), the results were different, see 'Sensitivity analysis for hydromorphone compared with morphine' below for further details. The type and number of other adverse events appeared to be balanced between groups in Hanna 2008 without any obvious differences. See Table 4 for a detailed account.

Data from Ma 2020 (measured during the three-month follow-up) found no clear evidence of a difference between groups for common adverse events including drug dependence, respiratory depression, pump-related problems, sensorimotor disorder, low intracranial pressure, cerebrospinal fluid leak, anorexia, catheter problems, dizziness, pruritus, vomiting, nausea, urinary retention, constipation and infections or pocket problems (P > 0.05). Only numerical data for constipation were extractable (RR 0.65, 95% CI 0.42 to 1.00; P = 0.05; Table 4).

Moriarty 1999 counted the number of adverse events that occurred within six days of treatment in each group (88 adverse events reported by 35 participants), therefore the data were not suitable for meta-analysis.

We rated the certainty of the evidence for specific adverse events as very low, downgrading twice for very serious study limitations and once for serious imprecision (Summary of findings 2). We decided not to downgrade for publication bias as the outcome had already been downgraded three times for other factors, therefore, further downgrading would be inappropriate.

3.4 Serious adverse events

Only one study reported the incidence of serious adverse events. There was no clear evidence of a difference between groups (RR 1.02, 95% CI 0.48 to 2.16; P = 0.96; Table 4) (Hanna 2008). We rated the certainty of the evidence for serious adverse events as very low, downgrading twice for very serious study limitations and once for serious imprecision.

3.5 Quality of life

One study was predefined to report quality of life in the protocol, but reported no data or results in the full text (Ma 2020).

3.6 Leaving the study early

One study (200 participants) reported leaving the study early within 24 days of treatment (Hanna 2008). There was no clear evidence of a difference between OROS hydromorphone and morphine sulphate (RR 1.42, 95% CI 0.95 to 2.12; Table 4). This study provided data for participants leaving the study early due to adverse events (15/99 with hydromorphone versus 11/101 with morphine) and lack of efficacy (11/99 with hydromorphone versus 4/101 with morphine), which also demonstrated no apparent difference.

One study (233 participants) reported leaving the study early at the end of three-month follow-up (Ma 2020). There was no clear evidence of a difference between hydromorphone and morphine (RR 0.97, 95% CI 0.89 to 1.05; P = 0.478; Table 4). This study provided data for participants leaving the study early due to discontinued intervention (25/121 with hydromorphone versus 26/112 with morphine), lost to follow-up (8/121 with hydromorphone versus 9/112 with morphine), changed to other therapy (13/121 with hydromorphone versus 13/112 with morphine), serious adverse events (4/121 with hydromorphone versus 4/112 with morphine), and death of cancer during trial (58/121 with hydromorphone versus 51/112 with morphine).

We rated the certainty of the evidence for leaving the study early as very low, downgrading twice for very serious study limitations and once for serious imprecision (Summary of findings 2). We decided not to downgrade for publication bias as the outcome had already been downgraded three times for other factors, therefore, further downgrading would be inappropriate.

3.7 Death

One study (200 participants) reported death that occurred within 24 days of treatment (Hanna 2008). There was no evidence of a difference between hydromorphone and morphine (RR 0.15, 95% CI 0.01 to 2.78; Table 4).

Another study (233 participants) reported death which occurred within three-month follow-up (Ma 2020). There was no evidence of a difference between hydromorphone and morphine (RR 1.05, 95% CI 0.80 to 1.39; P = 0.7143; Table 4).

We rated the certainty of the evidence for death as very low, downgrading for very serious study limitations (high risk of bias of other bias, incomplete data and reporting bias) and imprecision.

Sensitivity analysis for hydromorphone compared with morphine

In accordance with our protocol, we performed a sensitivity analysis for the adverse events data reported by Hanna 2008 comparing the effect size with and without dropouts. When we included dropouts in the analysis, we found a clear difference favouring the morphine group for confusion (RR 1.74, 95% CI 1.02 to 2.96), constipation (RR 1.56, 95% CI 1.12 to 2.17) and diarrhoea (RR 1.74, 95% CI 1.02 to 2.96). However, when we analysed completers data, only constipation remained clearly different (RR 1.76, 95% CI 1.09 to 2.87).

Comparison 4: hydromorphone compared with fentanyl

One study compared hydromorphone with fentanyl (Banala 2020).

4.1 Participant-reported pain intensity

Banala 2020 measured mean decreases of pain ratings (using an NRS) at 60 minutes after treatment initiation (Table 5). There was no evidence of a difference between hydromorphone and fentanyl in mean decrease from pain score at randomisation (MD −0.24, 95% CI −1.21 to 0.73; P = 0.63). In addition, there was no evidence of a difference in mean decrease from maximum pain score of 10 or from

randomisation pain score between groups (MD 0.81, 95% CI −0.18 to 1.80; P = 0.11).

We found no studies reporting the number of participants who achieved 'no worse than mild pain'.

We rated the certainty of the evidence for participant-reported pain intensity as very low, downgrading twice for very serious study limitations and once for serious imprecision (Summary of findings 3). We decided not to downgrade for publication bias as the outcome had already been downgraded three times for other factors, therefore, further downgrading would be inappropriate.

4.2 Participant-reported pain relief

The study did not report participant-reported pain relief.

4.3 Specific adverse events

The study did not report specific adverse events.

4.4 Serious adverse events

The study did not report serious adverse events.

4.5 Quality of life

The study did not report quality of life.

4.6 Leaving the study early

Banala 2020 reported the number of participants leaving the study early during treatment. There was no evidence of a difference between groups (RR 5.00, 95% CI 0.24 to 101.11; P = 0.294; Table 6). The study provided data for participants leaving the study early due to withdrawn consent (1/42 with hydromorphone versus 0/42 with morphine) and ineligible due to abnormal electrocardiograph (1/42 with hydromorphone versus 0/42 with morphine).

We rated the certainty of the evidence for leaving the study early as very low, downgrading twice for very serious study limitations and once for serious imprecision.

4.7 Death

The study did not report death.

DISCUSSION

Summary of main results

We included eight studies with 1283 participants in this review (data for 1181 participants available for analysis). Four studies compared hydromorphone with oxycodone, three studies compared hydromorphone with morphine and one study compared hydromorphone with fentanyl. Overall, the data demonstrated no clear evidence of a difference between groups for all comparisons; however, data were skewed, and we did not use meta-analysis for primary outcomes. Participants achieved no worse than mild pain in all included studies (Banala 2020; Hagen 1997; Hanna 2008; Inoue 2017; Inoue 2018; Ma 2020; Moriarty 1999; Yu 2014). For the safety of drugs, the risk of confusion, constipation and diarrhoea favoured the morphine group, and there was no clear evidence of a difference between groups for other specific adverse events (Table 2; Table 4). Regarding serious adverse events, there was no clear evidence of a difference between hydromorphone and oxycodone (Analysis 1.3), or hydromorphone and morphine (Table 4). The observed differences favouring morphine were questionable due to the instability of analysis caused by missing data from the trials. Hanna 2008 reported three deaths in the morphine group during the trial period, but trialists claimed that they were not related to the drug but were the consequences of cancer. Yu 2014 and Ma 2020 also reported death (Yu 2014: eight in the hydromorphone group and 16 in the oxycodone group; Ma 2020: 58 in the hydromorphone group and 51 in the morphine group), but the most common reason was disease progression. Inoue 2017 and Inoue 2018 reported serious adverse events (including deaths), but no specific number of deaths in each group. The two studies that contributed the most data in this review had over 10% dropout rates, but the reasons and proportion of dropouts were balanced between groups (Hagen 1997; Hanna 2008).

Moreover, we are aware that results from this review may indicate the difference between different dosages of opioid rather than different opioids. However, this review was not able to convert included treatments' dosage into any equivalent dose to a particular drug, such as morphine, to confirm this issue is due to the treatment dosage in the included studies which were mostly reported as a mean rather than a range. It would be difficult to give a precise equivalent dose to morphine. Therefore, the current conclusion was given in relation to different drugs.

In addition, opioid rotation is a common practice for the improvement of pain control or drug tolerability, or both (Quigley 2004; Schuster 2018). When these appropriate interventions have been exhausted or when adverse effects are rapid and severe (or both), rotation to an alternative opioid may help, but there is a lack of evidence to support rotation (Schuster 2018).

Overall completeness and applicability of evidence

There is a lack of data on children and younger adults for the use of hydromorphone for cancer pain. The mean age of participants included in this review was approximately 61 years. None of the studies stated the cancer stage. We were able to collect data on the primary outcome of no worse than mild pain and most of the secondary outcomes that we intended to measure, with the exception of quality of life. Applicability of the evidence was limited as the included studies compared only oxycodone, morphine and fentanyl with hydromorphone. Included studies were conducted in high-income countries, which may have limited generalisability in some lower-income countries.

There were no studies comparing hydromorphone with placebo. We found no published trials that compared hydromorphone with placebo regarding effectiveness and safety. It is very interesting since 'a randomised placebo-controlled' clinical trial is agreed as the 'gold standard' for testing efficacy and safety in people. It might be explained that current international guidelines suggest opioids dose equivalence to morphine, which might slightly encourage researchers to compare opioids with morphine. In addition, there are ethical issues with placebo controls in people with cancer pain. The current evidence included comparisons between hydromorphone and morphine, fentanyl and oxycodone, which may reflect its effectiveness and safety. Although the included studies in this review did not identify any placebo-controlled RCTs, we did identify an ongoing registered trial that is planning to compare hydromorphone with placebo.

There was heterogeneity within the included trials with respect to their study designs, formulations used and durations of follow-up. Two studies were cross-over design and two used a parallel design using two phases. All studies used CR or ER opioids, yet one study included an initial phase which used an IR formulation (Hanna 2008). The duration of follow-up between the trials ranged from five to 28 days. These factors increased the difficulty of drawing specific conclusions from the studies.

It is worth noting that two of the trials in this review used the OROS formulation of hydromorphone, which has some unique properties that differ from other formulations of hydromorphone (Hanna 2008, n = 200; Yu 2014, n = 260). It is a unique long-acting opioid formulation that utilises Push-Pull active osmotic technology and maintains consistent hydromorphone plasma concentrations throughout the 24-hour dosing interval, providing long-lasting analgesia (Angst 2001; Drover 2002; Palangio 2002). The dosage form controls the drug release into the body, almost independently from factors such as the surrounding pH or gastric motility (Bass 2002; Verma 2002). There is a minimal effect of food on the rate and extent of absorption of hydromorphone from OROS hydromorphone (Sathyan 2007). It has been reported that the pharmacokinetics of OROS hydromorphone are also minimally affected by alcohol. These unique features of OROS may further limit the generalisability of evidence. Similarly, we are aware of other formulations of hydromorphone (and other opioids), such as immediate release and sustained release formulation, which may have potential benefits for specific groups of people with cancer, but we found no evidence for these as part of this review.

Noteworthy, none of the eight included studies reported participants' quality of life. One study planned to measure quality of life in the protocol, but no outcomes were identified in the published report. It is clear that people with cancer who experience pain may face some psychological problems, social adverse effects, and eventually, a poor quality of life. Therefore, the absence of quality of life evidence may indicate a research gap in people with cancer pain.

Quality of the evidence

We judged all eight studies at high risk of bias overall because they all had at least one domain with high risk of bias.

The two most prominent risks of bias concerned sample size and sponsorship. One of the studies only had 44 participants (Hagen 1997), and six studies were either funded or conducted by industry (Banala 2020; Hagen 1997; Hanna 2008; Inoue 2017; Inoue 2018; Moriarty 1999). One study was at high risk overall due to selective reporting and high attrition rate (Ma 2020). The certainty of the body of evidence was very low, mainly due to the high risk of bias judged due to pharmaceutical company sponsorship and potential conflict of interest, as well as imprecision around effect estimates. Although the certainty may be downgraded also for inconsistency and publication bias, no further actions were taked since the the outcomes had already been downgraded three times for other factors. High attrition rate also played a role in downgrading the overall certainty of the evidence. See Summary of findings 1; Summary of findings 2; and Summary of findings 3 for detailed assessment results of each individual outcome. The current body of evidence identified does not allow a robust conclusion, as most data for the outcomes were either skewed or had wide CIs around the estimated effect size.

Potential biases in the review process

Although we searched mainstream biomedical databases and clinical trials registries, searches beyond these resources to include other non-English literature may improve the comprehensiveness of the search results. Two review authors independently performed screening and data extraction, but we were unable to extract any numerical data from Moriarty 1999, which may have had some influence on the results.

Agreements and disagreements with other studies or reviews

The current review indicated little difference between hydromorphone and three other opioids, oxycodone, morphine and fentanyl, in terms of analgesic efficacy. This finding is consistent with the 2012 European Association for Palliative Care (EAPC) guidelines (Caraceni 2012), which included a series of systematic reviews of the evidence for opioids in people with moderate to severe cancer pain (Caraceni 2011; King 2011a; King 2011b; Pigni 2011). The reviews concluded that there is a lack of evidence to demonstrate superiority or inferiority of hydromorphone in comparison with other analgesics and EAPC made a weak recommendation that hydromorphone, morphine, oxycodone or fentanyl could be used as the first choice for step three of the WHO analgesic ladder. Wiffen 2017a conducted an overview of reviews investigating the effect of opioids for cancer pain. The study also found that the amount and quality of evidence on using opioids for the treatment of cancer pain is generally very low, and current evidence provides little information on whether there are any differences in effectiveness and adverse events between different types of opioids. The study also concluded that most people will experience adverse events after taking opioids, and the more common adverse events are constipation and nausea (Wiffen 2017a). The proportion of people experiencing intolerable adverse events is around 1/10 or 2/10, which may lead to a change in treatment. In our review, the most common specific adverse events of hydromorphone were also constipation (52/99 participants) and nausea (37/99 participants). The risks of specific adverse events higher than 20% were constipation (53%), nausea (37%), somnolence (30%), confusion (29%), diarrhoea (29%), vomiting (29%), asthenia (28%), anxiety (27%), insomnia (27%), dizziness (26%), fatigue (26%), pyrexia (26%), anaemia (25%), headache (25%), pruritus (25%), anorexia (24%) and peripheral oedema (23%). The incidence of serious adverse events of hydromorphone was around 8% to 12%.

The results of this review do not differ from the results of the previous Cochrane Review (Bao 2016; Quigley 2003).

AUTHORS' CONCLUSIONS

Implications for practice

For people with cancer pain

Based on data gathered from the eight included trials, it appears that hydromorphone has a similar effect on participant-reported pain intensity as oxycodone, morphine and fentanyl for adults with moderate to severe cancer pain. There was no evident comparative difference in analgesic effect between hydromorphone and other opioids investigated in this review and the mean postintervention pain scores were generally below the threshold for 'no worse than mild pain' on all investigated treatments. There were several

adverse events, but generally there was no difference between groups. In summary, there is no clear evidence of a difference between hydromorphone and oxycodone, morphine or fentanyl in adults with moderate to severe cancer pain. However, this finding should be applied with caution for our review included only eight studies, which had different designs and limited sample sizes. The evidence of the benefits and harms of hydromorphone compared with oxycodone, morphine and fentanyl is very uncertain. There were no data available for children or for some important outcomes such as quality of life.

For clinicians

Based on eight included trials with different designs and limited number of participants, we found a lack of evidence to support a preference for hydromorphone over other opioid analgesics such as morphine, oxycodone and fentanyl. The treatment effect of hydromorphone appeared to be similar to that of the comparator drugs for adults with moderate to severe cancer pain. There were minor adverse events in all treatment groups and generally no clear evidence of a difference between groups. However, most of the outcome data were based on single randomised controlled trials with small sample sizes, thus the findings of the current review should be interpreted and applied with caution. We found no data for children. The insufficient evidence requires clinicians to balance potential benefits against potential adverse events on the merit of each individual case when recommending treatment in clinical practice.

For policy makers

This review identified little evidence to support hydromorphone as the first-, second- or third-line treatment for cancer pain. However, evidence collated in the current review suggests hydromorphone has a similar analgesic effect as morphine, oxycodone and fentanyl, it can be considered as an alternative when other opioids result in excessive adverse events such as sedation and respiratory depression, and when people with cancer pain experience renal failure. We found no data for children. Included studies were conducted in high-income countries, which may compromise the external validity of the review as some of the drugs investigated may have limited accessibility in some lower-income countries. Finally, it is worth noting that findings from the current review are mainly based on small trials with different designs and limited sample size and some risk of bias, therefore, should be applied with caution.

Implications for research

This review confirms a general lack of research in this subject area, with poor and inconsistent reporting of adverse events and low trial sizes. Wiffen 2017a suggest some core outcomes that can help decisions in clinical practice, for instance, the proportion of participants reporting no worse than mild pain on treatment by 14 days after start of treatment, Patient Global Impression of Change (PGIC) of much or very much improved. These outcomes are seldomly reported by the included studies. Future trials with significant numbers of participants (e.g. more than 200 per treatment arm) are needed to evaluate important outcomes of hydromorphone for the management of moderate to severe cancer pain in adults. Future research is encouraged to involve children and young adults to provide direct evidence in this population. Further adequately powered randomised controlled trials should use standardised tools or scales to measure pain as a primary outcome. More data on other secondary outcomes, as well as the comparative effect of a more comprehensive range of medications, would also be useful to enable the review to draw a more reliable and conclusive effect. Longer-term toxicity data should be collected if possible.

Prevalence of sleep disturbance in people with cancer ranges from 24% to 95% (Graci 2005; Mercadante 2004), and is more common among females with cancer, older people, and people with depression or anxiety (Akechi 2007; Graci 2005). Therefore, we suggest that more attention is given to pain control for increasing quality of sleep and quality of life (Graci 2005; Kvale 2006), especially the effect of OROS (osmotic-controlled release oral delivery system) hydromorphone for people with cancer pain with sleep disturbance. The absence of the outcome quality of life may indicate a research gap in the field. Further high-quality randomised controlled trials are expected to define quality of life as an important outcome in trials.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Banala 2020

Study characteristics	
Methods	Allocation: randomised Blindness: open label Duration: 1 hour Funding: DepoMed, Inc to SJY. DepoMed has been acquired by Assertio, Inc; partially supported by The University of Texas MD Anderson Cancer Center Support Grant Setting: US, single centre, emergency department setting Design: parallel
Participants	Diagnosis: people with severe cancer pain (rated ≥ 7 on a 0–10 NRS, where 0 = 'no pain' and 10 = 'pain as bad as you can imagine') n = 84 Age: 22–84 years Sex: 36 men; 46 women Cancer stage: not reported History: not reported Inclusion criteria: people with severe pain (rated ≥ 7 on a 0–10 NRS, where 0 = 'no pain' and 10 = 'pain as bad as you can imagine') and had been on opioid therapy for ≥ 1 week (oral morphine ≥ 60 mg/day,

Banala 2020 *(Continued)*

	transdermal fentanyl 25 µg/hour, oxycodone 30 mg/day, oral hydromorphone 8 mg/day, oral oxymorphone 25 mg/day, or an equianalgesic dose of another opioid) Exclusion criteria: chronic active hepatitis, cirrhosis, or hepatic encephalopathy; known or suspected hypersensitivity or intolerance to fentanyl, hydromorphone or excipients in the study medications; sinusitis, obstruction of nasal passages, nasopharyngeal cancer, paranasal sinus malignancies, or any conditions in the nasopharyngeal area that could affect absorption of intranasal fentanyl spray; having taken oral IR opioids within 4 hours prior to arrival in the emergency department; and previous participation in this trial; pregnant, breastfeeding or intending to become pregnant
Interventions	• Hydromorphone, 1.5 mg IV at time 0 (defined as the time of completion of opioid IV push) with a rescue dose allowed at 0.5 hour; n = 42 (40 completed study) • Fentanyl, nasal spray 100 µg delivered at time 0 (defined as the time when intranasal fentanyl spray was administered) with a rescue dose allowed at 0.5 hour; n = 42 (42 completed study) Study nurse called participant 24 hours after participation to ask about adverse events since taking part in the study.
Outcomes	Pain intensity NRS[a] Dropouts
Notes	[a]Treatment initiation (T0) pain ratings were unavailable; therefore, the authors estimated T0 pain by comparing 1. T60 ratings, assuming similar group T0 ratings; 2. pain change, estimating T0 pain = randomisation ratings, and 3. pain change, with T0 pain = 10 (hydromorphone group) or T0 pain = randomisation rating (fentanyl group). Funded by pharmaceutical company.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "This was a single-center, randomized, open-label clinical trial designed to compare IN fentanyl versus IV opioids in pain intensity reduction by 1 hour after drug delivery" (page 3). Comments: authors only stated that participants were randomised, no further details.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study designed with open label, so assumed to have no blinding settings.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	No information provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants in the hydromorphone dropped out with the reasons provided clearly; attrition rate was 2%.
Selective reporting (reporting bias)	Low risk	All predefined outcomes in protocol were reported.

Banala 2020 *(Continued)*

Other bias	High risk	Funding from commercial pharmaceutical company.

Hagen 1997

Study characteristics	
Methods	Allocation: randomised Blindness: double-blind, double-dummy Duration: pre-cross-over phase: 7 days in each phase. Total study duration 14 days Funding: 'Purdue Frederick,' since renamed 'Purdue Pharma' Setting: Canada. Unclear if these were inpatients or community patients Design: cross-over
Participants	Diagnosis: people with chronic cancer pain and stable analgesic requirements n = 44 (31 analysed) Age (mean): 56 (SD 3) years Sex: 13 men; 18 women Cancer stage: not reported History: of the 31 participants who completed the study, location of primary tumour was breast (7), colorectal (5), lung (1), urological/prostate (5), central nervous system (4), unknown primary site (2) and other (7) Inclusion criteria: people with chronic cancer pain and stable analgesic requirements Exclusion criteria: known hypersensitivity to opioid analgesics; intolerance of oxycodone or hydromorphone; presence of a medical or surgical condition likely to interfere with drug absorption in the gastrointestinal tract; concurrent use of other opioid analgesics during the study period; presence of intractable nausea or vomiting; people who had undergone or were expected to undergo therapeutic procedures likely to influence their pain during study period. Consent: "The study protocol and informed consent form received scientific and ethical approval, and patients gave written informed consent before participating in the study" (page 1429)
Interventions	• Hydromorphone CR, dose unknown (mean daily dose reported as 24 (SD 4) mg); n = 22 (19 completed study) • Oxycodone CR, dose unknown (mean daily dose reported as 120 (SD 22) mg); n = 22 (12 completed study) Each intervention was administered every 12 hours for 7 days pre-cross-over. No other opioids permitted. Non-opioid analgesics that had been part of the person's treatment before the study were permitted. Incident and non-incident breakthrough pain was treated with IR oxycodone and hydromorphone matching the active opioid analgesic at a dosage of approximately 10% of the daily scheduled opioid dose.
Outcomes	Pain intensity VAS[a] Pain intensity ordinal[a] Sedation VAS[a]

Hagen 1997 *(Continued)*

	Nausea VAS[a]
	Dropouts[a]
	Unable to use:
	Frequency of rescue analgesic use was not reported as there were no pre-cross-over data.
Notes	[a]Unpublished data obtained from Purdue Pharma.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	The author stated the study was a randomised controlled trial, however, there was no further information on the method used to generate random sequence. Therefore, we rated this as unclear risk due to insufficient reporting.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although the outcome assessment was not reported, as most of outcomes were participant-reported, we rated this as low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	Data only analysed for 31/44 participants. Dropout rate > 10%.
Selective reporting (reporting bias)	Low risk	The protocol was not available. All outcomes in the method section were reported.
Other bias	High risk	Notable concerns: pharmaceutical company-funded.

Hanna 2008

Study characteristics

Methods	Allocation: randomised
	Blindness: double-blind
	Duration: up to 24 days
	Funding: Johnson & Johnson (previously ALZA Corporation)
	Setting: multi-centre (37 centres in Belgium, Canada, France, Germany, the Netherlands, Spain, Sweden and the UK); inpatients, outpatients and day patients
	Design: parallel
Participants	Diagnosis: people with moderate to severe chronic cancer pain requiring 60–540 mg of oral morphine (or equivalent) every 24 hours

Hanna 2008 *(Continued)*

	n = 200 Age (mean): 59.8 years Sex: 98 men (49%); 102 women (51%) Cancer stage: not reported History: cancer type: breast (56), lung (39), genitourinary (30), gastrointestinal (32), oral cavity (6), lymphoma (3), leukaemia (3), bone (2) and other (29) Inclusion criteria: inpatients, outpatients and day patients ≥ 18 years of age; moderate to severe chronic cancer pain; currently receiving strong oral or transdermal opioid analgesics (60–540 mg of oral morphine or equivalent every 24 hours); appropriate candidate for strong oral or transdermal analgesics (anticipated requirement, 60–540 mg of oral morphine or equivalent every 24 hours); pain suitable for treatment with a once-daily formulation Exclusion criteria: pain not considered potentially responsive to opioids; pain present only upon movement; need for other opioid analgesics (except study medication and breakthrough pain medication) after randomisation; current or recent (within 6 months) history of drug or alcohol abuse (or both); pregnant or lactating, seeking pregnancy or failing to take adequate contraceptive precautions; intolerance of, or hypersensitivity to, hydromorphone or other opioids; presence of gastrointestinal disease of sufficient severity to likely interfere with oral analgesia (e.g. dysphagia, vomiting, no bowel movement or bowel obstruction due to impaction within 5 days of study entry, severe gastrointestinal tract narrowing that may have affected analgesic absorption or transit); use of monoamine oxidase inhibitors within 2 weeks prior to study entry; investigational drug use within 4 weeks of study entry; presence of conditions for which risks of opioid use outweigh potential benefits (e.g. raised intracranial pressure, hypotension, hypothyroidism, asthma, reduced respiratory reserve, prostatic hypertrophy, hepatic impairment, renal impairment, older and debilitated people, convulsive disorders, Addison's disease) Consent: "All patients who entered the trial were informed of the nature of the study, and provided written informed consent for participation. The study was conducted in accordance with the principles of the Declaration of Helsinki."
Interventions	• Hydromorphone IR 12–108 mg/day; dose titrated to next higher dose level if participant had > 3 breakthrough pain episodes requiring pain medication within the previous 24 hours, maximum once a day, dose titration continued until dose-stable pain* control achieved; n = 99 • Morphine IR 62–540 mg/day, dose titrated to next higher dose level if participant had > 3 breakthrough pain episodes requiring pain medication within the previous 24 hours, maximum once a day, dose titration continued until dose-stable pain[a] control achieved; n = 101 Initial IR phase and subsequent SR phase: • IR phase: formulations of either hydromorphone (Dilaudid, Abbott Laboratories) or morphine (morphine sulphate IR (Sevredol, Napp Laboratories)) every 4 hours (6 times daily) for 2–9 days. Individual dose levels based on participant characteristics and selected according to available tablet strength and a working conversion ratio of 1:5 (1 hydromorphone: 5 morphine equivalence). Concomitant chemotherapy or radiotherapy was permitted • SR phase: duration 10–15 days: same drugs received but in SR formulation (OROS hydromorphone, once daily, or CR morphine (morphine sulphate SR (MST Continus, Napp Laboratories)), twice daily. Same starting dose level as dose-stable pain achieved in IR phase, adjusted as required every 2 days at most [a]Dose-stable pain control: defined as participants who experience 2 consecutive days with ≤ 3 breakthrough pain episodes requiring rescue medication – they could then begin SR phase of the study. Participants not achieving dose-stable pain control by day 9 were withdrawn from the study.
Outcomes	Pain ('worst pain in the past 24 hours' item of the BPI) Adverse events
Notes	

Hanna 2008 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants randomised 1:1, with a central computer-generated randomisation list.
Allocation concealment (selection bias)	Low risk	There was no explicit description on allocation concealment, but we considered concealment was likely to have been used since the randomisation was done via a central list.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although the outcome assessment was not reported, as most of the outcomes were participant-reported, we rated this item as low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	Withdrawals from study were addressed. Quote: "All efficacy variables were analyzed using the intent-to-treat (ITT) population, which included all patients who took at least one dose of study medication and had at least one assessment from each study phase." The proportion of dropouts appeared higher in hydromorphone group; however, the reasons for dropout were comparable between groups, thus we considered the proportional difference between groups was unlikely to have had an effect on effect estimate. However, because the dropout rate was > 10%, we rated this domain as high risk.
Selective reporting (reporting bias)	Low risk	The study protocol was available. All measured outcomes were reported except 2 that were not relevant to this review.
Other bias	High risk	Notable concerns: pharmaceutical company-funded 1 study author was employed by Johnson & Johnson (study sponsor).

Inoue 2017

Study characteristics

Methods	Allocation: randomised Blindness: double-blind, double-dummy Duration: drugs received for 7 days, measures conducted at completion or discontinuation of treatment, did not mention duration of study Funding: Daiichi Sankyo Co, Ltd Setting: multi-centre (49 institutions in Japan); unclear if these were inpatients or community patients Design: parallel
Participants	Diagnosis: people with moderate to severe cancer pain requiring treatment with potent opioid analgesics

Inoue 2017 *(Continued)*

	n = 181 Age (mean): 69.2 (SD 9.7) years Sex: 108 men (60.7%); 70 women (39.3%) Cancer stage: not reported History: cancer type: breast (12), lung (56), gastrointestinal (65), hepatic-biliary-pancreatic (27), urogenital (16) and other (2) Inclusion criteria: people with cancer aged ≥ 20 years; receiving non-opioid analgesics for cancer pain who had not used opioid analgesics within 2 weeks prior to enrolment; VAS score (mean pain within the last 24 hours) ≥ 35 mm (moderate to severe pain that interfered with functioning); Eastern Cooperative Oncology Group performance status ≤ 3 Exclusion criteria: presenting with symptoms for which oxycodone or morphine were contraindicated or relatively contraindicated; receiving a monoamine oxidase inhibitor within 14 days prior to enrolment; participating in another clinical trial within 28 days prior to enrolment; serious hepatic, renal or respiratory disorder of Common Terminology Criteria for Adverse Events grade 3 Consent: "Written informed consent was obtained from all subjects prior to study participation. The study was approved by the institutional review board of each study site and carried out in compliance with ethical principles based on the Declaration of Helsinki and Good Clinical Practice."
Interventions	• Hydromorphone ER 4 mg/day + placebo ER: dose could be increased in 5 stages up to a maximum hydromorphone 24 mg/day, once-daily orally; the initial dose of hydromorphone 4 mg/day that was assumed to be equivalent to morphine 20 mg/day on the basis of the 5-fold higher efficacy ratio of hydromorphone compared with morphine; n = 88 • Oxycodone ER 10 mg/day + placebo ER: dose could be increased in 5 stages up to a maximum oxycodone 80 mg/day, twice-daily orally; the initial dose of oxycodone 10 mg/day that was specified as the dose for opioid-naive people in the Japanese package insert; n = 93 Investigators were allowed to increase the doses of the study drugs every 24 hours during the treatment period if necessary due to insufficient analgesic efficacy. Treatment was switched to appropriate analgesics after completion of study treatment, and participants were followed up. Oral morphine hydrochloride solution was used for rescue analgesia to avoid using the investigational agents for rescue. The IR preparations of hydromorphone and oxycodone faced challenges of being unapproved and potential confounding of safety assessments, respectively. Concomitant use of monoamine oxidase inhibitors, opioid analgesics, and narcotic antagonists was prohibited. In addition, starting new treatment with/changing the dosing regimen of systemic non-opioid analgesics, adjuvant analgesics for pain relief, bisphosphonates, or anti-RANKL antibody preparations was prohibited. It was prohibited for participants to undergo radiotherapy, nerve block, percutaneous vertebroplasty, or surgery, or receive any new cancer chemotherapy or immunotherapy for the first time. Magnesium oxide 2 g/day and prochlorperazine maleate 15 mg/day were administered to all participants to ensure balanced evaluation of constipation and nausea/vomiting.
Outcomes	Pain intensity VAS Adverse events[a] Leave study early Unable to use: Sleep quality, analgesia improvement rate, laboratory and clinical assessment[b] Severity of adverse events[c] *Narrative outcome:*

Inoue 2017 *(Continued)*

	Serious adverse events[d]: 11/88 participants in hydromorphone group (incidence rate 12.5%) and 14/92 participants in oxycodone group (incidence rate 15.2%)
Notes	[a]Investigators coded the AEs by system organ class and preferred terms based on the MedDRA (Medical Dictionary for Regulatory Activities, version 18.1. [b]Not predefined in protocol. [c]Severity of AEs was rated on a 3-grade scale (mild, moderate, and severe), no data reported. [d]Serious adverse events, including death, but no specific data for death. We contacted the authors of Inoue 2017 and Inoue 2018 to confirm they were different studies with different samples. The authors of these 2 studies replied in June 2020 and confirmed that they were 2 separate studies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomised at a ratio of 1:1, no other details provided.
Allocation concealment (selection bias)	Unclear risk	No information provided.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind; a double-dummy method was used for blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although the outcome assessment was not reported, as most of outcomes were participant-reported, we rated this item at low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	3/181 randomised participants dropped out, 2 in the hydromorphone group and 1 in the oxycodone group; dropout rate < 10%.
Selective reporting (reporting bias)	Low risk	Although the authors did not report all predefined outcome data that they planned to measure, for instance, analgesia improvement rate, severity of adverse events, laboratory and clinical assessment, these outcomes are not relevant, so we rated this item at low risk of bias.
Other bias	High risk	Notable concerns: pharmaceutical company-funded. Three authors (SI, AI and YK) were employees of the funding drug company.

Inoue 2018

Study characteristics

Methods	Allocation: randomised Blindness: double-blind, double-dummy Duration: received drugs for 5 days Funding: Daiichi Sankyo Co, Ltd

Inoue 2018 *(Continued)*

	Setting: multi-centre (50 sites in Japan); unclear if these were inpatients or community patients Design: parallel
Participants	Diagnosis: people with moderate to severe cancer pain requiring treatment with potent opioid analgesics n = 181 Age (mean): 67.3 (SD 10.19) years Sex: 116 men (67.4%); 56 women (32.6%) Cancer stage: not reported History: cancer type: head/neck (2), lung (63), breast (4), gastrointestinal (50), hepatic-biliary-pancreatic (22), urogenital (20) and others (11) Inclusion criteria: people with cancer aged ≥ 20 years; receiving non-opioid analgesics for pain relief who had not used opioid analgesics within 2 weeks of registration; the mean pain within the last 24 hours, measured by VAS, was ≥ 35 mm; Eastern Cooperative Oncology Group performance status ≤ 3 Exclusion criteria: presenting with symptoms for which oxycodone or morphine were contraindicated or relatively contraindicated; receiving a monoamine oxidase inhibitor within 14 days of registration; participating in another clinical trial within 28 days of registration; serious hepatic, renal or respiratory disorder of Common Terminology Criteria for Adverse Events grade 3 Consent: "The study was approved by the institutional review board of each study site and was conducted in compliance with ethical principles based on the Declaration of Helsinki and Good Clinical Practice. Written informed consent was obtained from all patients prior to study participation."
Interventions	• Hydromorphone + placebo: 4 times daily for 5 days, initial dose hydromorphone 4 mg/day and set based on 1–2 mg per dose as specified by the WHO, when a dose increase was deemed necessary during study drug administration, the dose could be increased up to the fourth dose (hydromorphone 16 mg/day) by 1 step every 24 hours; n = 92 • Oxycodone hydrochloride powder + placebo tablet: 4 times daily for 5 days, initial dose oxycodone 10 mg/day and was stipulated in the Japanese package insert for opioid-native patients, when a dose increase was deemed necessary during study drug administration, the dose could be increased up to the fourth dose (oxycodone 60 mg/day) by 1 step every 24 hours; n = 89 This dosage frequency was selected based on the standard pharmacokinetic profile for IR hydromorphone (i.e. onset of action in about 30 minutes and duration of action about 4 hours). Treatment was switched to appropriate analgesics after completion of study drug administration and after the post-study observation. Oral morphine hydrochloride solution was used as rescue medication for both groups. The following were prohibited throughout the study: coadministration of a monoamine oxidase inhibitor, opioid analgesic or narcotic antagonist; new administration of systemic non-opioid analgesics; supplementary analgesics; bisphosphonates; anti-RANKL antibody preparations; changes in dosage and administration; new initiation of radiotherapy, nerve block, percutaneous vertebroplasty, surgery or cancer chemotherapy or immunotherapy. Magnesium oxide 2 g/day and prochlorperazine maleate 15 mg/day were administered to all participants to ensure adequate control of constipation and nausea/vomiting and to enable appropriate safety evaluations.
Outcomes	Pain intensity VAS Adverse events Leaving the study early Unable to use:[a] Sleep quality, laboratory data, vital signs, and 12-lead electrocardiogram

Inoue 2018 *(Continued)*

	Narrative outcome: Serious adverse events:[b] 7/88 in hydromorphone group (incidence rate 8.0%); 8/84 in oxycodone group (incidence rate 9.5%)
Notes	[a]Not predefined in protocol. [b]Serious adverse events, including death, but no specific data for death. We contacted the authors of Inoue 2017 and Inoue 2018to confirm they were different studies with different samples. The authors of these 2 studies replied in June 2020 and confirmed that they were 2 separate studies.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated 1:1 to either group by computer-generated block random allocation sequence.
Allocation concealment (selection bias)	Low risk	There was no explicit description on allocation concealment, but we considered concealment was likely to have been used since the randomisation was done via a central list.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind, double-dummy.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although the outcome assessment was not reported, as most of the outcomes were participant-reported, we rated this item at low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	9/181 participants loss to follow-up, rate < 10%; the dropout rate for each group was similar.
Selective reporting (reporting bias)	Low risk	No information was provided on protocol. Therefore, we judged this domain by outcomes listed in the methods section. Although the author did not report data of the following outcomes, sleep quality, laboratory data, vital signs, and 12-lead electrocardiogram, they were not relevant to this review. So we rated this item at low risk of bias.
Other bias	High risk	Notable concerns: pharmaceutical company-funded; 3 authors were employees of the company.

Ma 2020

Study characteristics

Methods	Allocation: randomised Blindness: single-blind, block random coding table Duration: 12 weeks Funding: 'Chinese association for the study of pain, the minimally invasive interventional group,' research organisation

Ma 2020 *(Continued)*

	Setting: China; multi-centre, unclear about the settings Design: parallel
Participants	Diagnosis: Chinese people with moderate to severe cancer pain (mean pain intensity ≥ 5/10 cm on the VAS or breakthrough pain ≥ 3 times a day). n = 233 Age: 18–80 years Sex: 152 men; 81 women Cancer stage: not reported History: not reported Inclusion criteria: people with cancer pain aged 18–80 years; after standard treatment and opioid rotation according to the guidelines, oral morphine equivalent daily dose still > 200 mg with unsatisfactory analgesia or people with intolerable adverse effects caused by systemic opioids; mean pain intensity ≥ 5/10 cm on the VAS or breakthrough pain ≥ 3 times a day; people suitable for IDDS and with the ability to comply with the medical protocol and visit; and people with the indication of IDDS Exclusion criteria: with severe infection, respiratory dysfunction, serious liver dysfunction or renal dysfunction; history of allergy to narcotics or malignant hyperthermia; spinal deformation who are unable to receive the IT delivery system; intracranial metastasis, consciousness disorders, central nervous system infection or coagulation disorders; pregnant or lactating; plan to become pregnant within 1 month after the study; participated in another medical trial within 3 months before this study; family members of the study investigators; and people considered ineligible for the study as evaluated by the investigator
Interventions	• Hydromorphone IT, mean starting daily infusion dose (mean reported as 0.276 (SD 0.53) mg; n = 121 (121 completed study, 13 completed follow-up) • Morphine IT, mean starting daily infusion dose (mean reported as 1.551 (SD 4.20) mg; n = 112 (112 completed study, 9 completed follow-up) The starting infusion rates for IT opioids was based on the baseline oral morphine equivalent daily dose (pre-IDDS consumption) of each participant, 1:300 for IT: oral equivalent dose, and the opioid equivalence of hydromorphone to morphine was set at 0.15:1 according to the 2016 National Comprehensive Cancer Network guideline (1.5:10, for parenteral dose). For breakthrough cancer pain, the bolus dose of each participant was set at 1/10 of the daily continuous infusion dose individually. If the participant's previous 24-hour bolus press number was ≥ 4 times, daily continuous infusion dose increased according to the experience of the study physician; each time, it was increased by 50% of the previous 24-hour IT opioid daily dose, and then reset the bolus dose according to the daily continuous infusion dose. The participants were not allowed to intake any additional analgesics except the IT participant-controlled analgesia bolus doses of hydromorphone or morphine for the management of breakthrough pain. If the participant was diagnosed with neuropathic pain, they followed the study protocol, and the participant would not have received any other treatment except IDDS with hydromorphone/morphine. And according to the existing evidence and clinical experience, IT opioids could also be used for the treatment of neuropathic pain, although it was not the guideline recommendation.
Outcomes	Pain intensity VAS Clinical success rate Dropouts Unable to use: Quality of life measured by the quality of life score (36-item Short Form)[a], Drug cost-effectiveness[b], The frequency, duration and degree of the flare pain[b], Intensity of anxiety experienced by patient[b], Intensity of depression experienced by patient[b]

Ma 2020 *(Continued)*

Notes	[a]No available data. [b]Not predefined by protocol.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "A total of 233 participants across all centers were randomized chronologically in a 1:1 ratio according to the block random coding table and given the corresponding medication" (page 2503). Comments: participants were randomly assigned using random coding table.
Allocation concealment (selection bias)	Low risk	There was no explicit description on allocation concealment, but we considered concealment was likely to have been used since the randomisation was done via a random table.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "All patients and investigators conducting follow-up work were blinded to the treatment drug assignment throughout the study." Comments: although the report stated the trial was a single-blind study, participants and investigators were blinded, so we judged it at low risk.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although the outcome assessment was not reported, as most of the outcomes were participant-reported, we rated this item at low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	Although the report stated that 'all patients completed assessments of [primary and secondary outcomes],' the CONSORT flow diagram showed a total of 211/233 (90%) participants dropped out in the follow-up period. Therefore, we rated this at high risk.
Selective reporting (reporting bias)	High risk	The study protocol was available, but data on quality of life were not available.
Other bias	Unclear risk	Not obvious.

Moriarty 1999

Study characteristics

Methods	Allocation: randomised Blindness: double-blind, double-dummy Duration: 6 days (with run-in period of 1–3 days) Funding: Napp Laboratories Ltd Setting: not stated. Unclear if these were inpatients or community patients Design: cross-over
Participants	Diagnosis: people with cancer pain n = 100

Moriarty 1999 *(Continued)*

	Age: not stated Sex: 53 men; 47 women Cancer stage: not reported History: most common of primary malignancies presented by participants were lung, breast, gastrointestinal and genitourinary Inclusion criteria: people aged ≥ 18 years, with cancer and achieving pain control with CR morphine sulphate Exclusion criteria: significant respiratory depression; severe renal or hepatic impairment; taking strong opioid analgesics other than 12-hourly morphine sulphate; taking monoamine oxidase inhibitors currently or within the previous 2 weeks; pregnant (or not adequately protected from becoming pregnant) or lactating women Consent: no details
Interventions	• Hydromorphone CR 4 mg • Morphine CR 30 mg
Outcomes	Pain VAS Adverse events Treatment preference Use of rescue medication
Notes	No pre-cross-over data available. No contact details available to request necessary information. We are also unclear about the intensity of people's cancer pain. This review only intended to include people with moderate to severe cancer pain.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "… according to a randomisation schedule previously prepared by the clinical supplies department at Napp Laboratories Limited …" Comment: third-party randomisation used and was likely to be at low risk of bias.
Allocation concealment (selection bias)	Low risk	Third-party randomisation used, thus we considered allocation concealment was likely to have been done.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Matched placebos were taken throughout to maintain the blinding of the study (double-dummy technique)."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although the outcome assessment was not reported, as most of the outcomes were participant-reported, we rated this item at low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 people left the study early and were not included in the final analysis. Although the dropout rate was marginally > 10%, it is unlikely to have had a biased effect on the results, as reasons and proportion for dropout were given and comparable between groups.

Moriarty 1999 *(Continued)*

Selective reporting (reporting bias)	Low risk	No protocol registration information provided. All outcomes in the method section were reported.
Other bias	High risk	Notable concerns: pharmaceutical company-funded; 1 study author was an employee of Napp Laboratories Ltd, a pharmaceutical company that produces analgesics.

Yu 2014

Study characteristics	
Methods	Allocation: randomised Blindness: double-blind Duration: 3-phase study: screening period up to 14 days prior to randomisation; dose titration phase up to 8 days, and a 28-day dose maintenance phase Funding: not stated Setting: China. Unclear if these were inpatients or community patients Design: parallel
Participants	Diagnosis: Chinese people with moderate to severe cancer pain n = 260 Age: 18–70 years (range); 53.1±10.79 (mean±SD) Sex: men and women Cancer stage: not reported History: most common of primary malignancies presented by people were lung, breast, gastrointestinal and genitourinary Inclusion criteria: people who required or were expected to require 40–184 mg of oral morphine or morphine equivalents every 24 hours for chronic management of cancer pain and people who were reasonably expected to achieve a stable dose of opioid study medication during the study Exclusion criteria: people with pure neuropathic pain or pain of unknown origin (where a mechanism or physical cause could not be identified); only had pain on movement or acute pain; required other opioid analgesics (apart from the morphine hydrochloride, in IR formulation, allowed as rescue medication for breakthrough pain); had any significant central nervous system disorder; risk of treatment with study medication could outweigh the potential benefits; women of childbearing potential who were pregnant or lactating Consent: written informed consent was obtained before entering the study
Interventions	• Hydromorphone ER (OROS hydromorphone) 8–32 mg; n = 130 • Oxycodone CR 10–40 mg; n = 130 The study completed a dose titration phase (up to 8 days), and a 28-day dose maintenance phase Dose titration phase: randomised participants were converted from their prior opioids to their morphine equivalents and titrated to adequate effect (as determined by the pain assessments and supplementary analgesic requirements), and dosage adjustments were made no more frequently than every 2 days. Upward and downward dose titrations were allowed, but the maximum total daily dose was not to exceed hydromorphone ER 32 mg or oxycodone CR 80 mg.

Yu 2014 *(Continued)*

	Participants had to achieve a stable dose providing pain control at least in the last 2 days of the titration phase (2–8 days) to be eligible to enter the maintenance phase. Maintenance phase: the titrated dose was continued for 28 consecutive days. Upward and downward dose titrations were not to exceed a total daily dose of hydromorphone ER 32 mg or oxycodone CR 80 mg.
Outcomes	BPI pain intensity Participant assessment of pain at its worst in the past 24 hours (assessed with BPI) Pain at its least in the past 24 hours Pain relief in the past 24 hours Adverse events, assessed with treatment-emergent adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "Central randomisation (1:1) by an online dynamic minimization allocation programme as the stratification factors was implemented." Comment: third-party central randomisation was used, thus was likely to be at low risk of bias.
Allocation concealment (selection bias)	Low risk	Quote: "Interactive web based response system designated a unique patient number and treatment code, which dictated the treatment assignment for each patient." Comment: judging from the above description, allocation was concealed by the third party who conducted randomisation.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Quote: "Hydromorphone ER, oxycodone CR and placebo were provided in the form of over-encapsulated tablets. Dosing had to start in the morning and the study drug was administrated twice daily, with placebo tablet substitute for 1 dose of hydromorphone ER to maintain blinding. The blinding was broken only if specific emergency treatment dictated knowing the treatment status." Comment: placebo was employed to mask blinding where necessary, thus was likely to be at low risk of bias.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although the outcome assessment was not reported, as most of the outcomes were participant-reported, we rated this item at low risk of bias.
Incomplete outcome data (attrition bias) All outcomes	High risk	137/260 participants completed the study, loss to follow-up > 10%.
Selective reporting (reporting bias)	Low risk	The study protocol was available and all predefined outcomes were reported.
Other bias	High risk	Notable concerns: pharmaceutical company-funded; the study sponsor was Johnson & Johnson Pharmaceutical Research & Development, LLC.

AE: adverse event; BPI: Brief Pain Inventory; CR: controlled release; ER: extended release; IDDS: intrathecal drug delivery system; IR: immediate release; IT: intrathecal; IV: intravenous; n: number of participants; NRS: numerical rating scale; OROS: osmotic-controlled release oral delivery system; SD: standard deviation; SR: slow release; VAS: visual analogue scale; WHO: World Health Organization.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Amsbaugh 2016	Not a randomised controlled trial.
Han 2014	Not a randomised controlled trial.
Lee 2012	Not a randomised controlled trial.
Wirz 2008	Not a randomised controlled trial. Participants who were already taking the experimental and control medications were randomly selected to be consented to take part in the study.
Wirz 2009	Not a randomised controlled trial. Participants who were already taking the experimental and control medications were randomly selected to be consented to take part in the study.
Yang 2018	People with pain after surgery, not predefined cancer pain in protocol.

Characteristics of studies awaiting classification *[ordered by study ID]*

ACTRN12605000696695

Methods	Randomised, parallel design
Participants	Moderate or severe pain
Interventions	Hydromorphone vs morphine sulphate tablets
Outcomes	Unclear
Notes	No access to the full text; therefore, we could not confirm whether details of the study met our inclusion criteria.

ChiCTR1900028015

Methods	Randomised, parallel design
Participants	Cancer pain
Interventions	Hydromorphone vs morphine
Outcomes	Pain intensity, pain relief rate
Notes	No access to the full text; therefore, we could not confirm whether details of the study met our inclusion criteria.

ChiCTR2000037845

Methods	Unclear
Participants	Cancer pain
Interventions	Hydromorphone vs oxycodone
Outcomes	Pain intensity
Notes	No access to the full text; therefore, we could not confirm whether details of the study met our inclusion criteria.

ChiCTR-IPR-17013446

Methods	Unclear
Participants	Cancer pain
Interventions	Hydromorphone vs morphine
Outcomes	Pain relief rate
Notes	No access to the full text; therefore, we could not confirm whether details of the study met our inclusion criteria.

CTRI/2009/091/000244

Methods	Randomised, open label, parallel design
Participants	Breakthrough pain
Interventions	Unclear
Outcomes	Adverse events, numerical pain score
Notes	No access to the full text; therefore, we could not confirm whether details of the study met our inclusion criteria.

EUCTR2004-005187-24-SK

Methods	Randomised, open label, parallel design
Participants	Severe pain
Interventions	Hydromorphone vs oxycodone
Outcomes	Unclear
Notes	No access to the full text; therefore, we could not confirm whether details of the study met our inclusion criteria.

EUCTR2008-002273-12-IT

Methods	Unclear
Participants	Oncological, chronic, neuropathic, nociceptive peripheral pain, or a combination of these
Interventions	Hydromorphone vs morphine vs oxycodone vs buprenorphine vs fentanyl
Outcomes	Unclear
Notes	No access to the full text; therefore, we could not confirm whether details of the study met our inclusion criteria.

JPRN-JapicCTI-142666

Methods	Unclear
Participants	Non-opioid analgesics for cancer pain
Interventions	Hydromorphone vs oxycodone
Outcomes	Pain intensity visual analogue scale
Notes	No access to the full text; therefore, we could not confirm whether details of the study met our inclusion criteria.

Characteristics of ongoing studies *[ordered by study ID]*

NCT00822614

Study name	The safety of fentanyl TAIFUN treatment after titrated dose administration and the current breakthrough pain treatment for breakthrough pain in cancer patients
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Blinding: open label Primary purpose: treatment
Participants	People with breakthrough cancer pain Inclusion criteria: aged ≥ 18 years; medically documented diagnosis of cancer; use of a fixed 24-dose of opioid as maintenance therapy with a dose equivalence of oral morphine of ≥ 60 mg/day, or transdermal fentanyl ≥ 25 µg/hour, or oral oxycodone ≥ 30 mg/day, or oral hydromorphone ≥ 8 mg/day; current opioid treatment for ≥ 7 days prior to randomisation; current use of opioid medication for breakthrough pain; ≥ 4 episodes of breakthrough pain per week, with peak intensity of ≥ 4 on the numerical pain scale at pain onset; ≤ 4 breakthrough pain episodes per day; peak inspiratory flow rate ≥ 20 L/minute; Karnofsky Performance Status ≥ 40; life expectancy ≥ 12 weeks; written informed consent

NCT00822614 *(Continued)*

	Exclusion criteria: uncontrolled or rapidly increasing breakthrough pain; symptomatic intracranial tumours or cerebral metastases; persistent symptomatic asthma; unable to use an inhaler; inadequate lung function, as defined by peak expiratory flow rate < 60%; hypersensitivities, allergies or contraindications to fentanyl or the study medication components; recent history of alcohol or substance abuse (in past 1 year); radiotherapy to the thorax within 30 days of the beginning of the titration phase; cognitive impairment or any neurological or psychiatric disease that could compromise the ability of the patient to complete the assessments; participation in any clinical study with an experimental drug within 30 days of randomisation; any clinical condition or medical history which, in the opinion of the investigator, would not allow for the safe completion of the study or the safe administration of the study drug; premenopausal women who are not surgically sterile or have a positive pregnancy test at baseline visit or are of child-bearing potential and are not using a reliable method of contraception or do not plan to continue using this method throughout the study or who are breastfeeding
Interventions	• Fentanyl TAIFUN • Opioid
Outcomes	Adverse events profile Safety Proportion of participants who can be titrated to an effective dose of fentanyl Efficacy Participant preference Sustained analgesic effect Follow-up 28 days
Starting date	December 2008
Contact information	Donna Fordham; Tel: +9 417 426 585; Email: fordhamd@akelapharma.com
Notes	Estimated completion date: January 2010; however, the study passed its completion date with no results released.

NCT02084355

Study name	Study efficacy and safety of opioid rotation compared with opioid dose escalation in patients with moderate to severe cancer pain – open label, randomized, prospective study
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Blinding: open label Primary purpose: supportive care
Participants	People with cancer pain Inclusion criteria: aged > 18 years; being treated with 1 strong opioid including oral oxycodone, oral hydromorphone or fentanyl patch of 60–200 mg of oral morphine equivalent daily dose; moderate to severe cancer pain (NRS > 3) at screening; uncontrolled adverse effects associated with currently applied opioid

NCT02084355 *(Continued)*

	Exclusion criteria: previous opioid rotation; unable to take oral medication; life expectancy < 1 month; newly started chemotherapy or radiotherapy (or both) within past 2 weeks of screening; serum AST, ALT or alkaline phosphatase > 2.5 times of upper normal limit; serum total bilirubin or creatinine > 1.5 times of upper normal limit
Interventions	• Oral oxycodone • Oral hydromorphone • Fentanyl patch
Outcomes	Not described in the registration record
Starting date	April 2014
Contact information	Se-Il Go; Tel: +82 55 750 9454 ext 9454; Email: gose1@hanmail.net
Notes	Estimated completion date: January 2016

NCT04243954

Study name	Intravenous vs oral analgesia in cancer patients with severe pain after successful titration
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: parallel assignment Blinding: open label Primary purpose: treatment
Participants	People with severe cancer pain Inclusion criteria: aged 18–80 years and diagnosed as malignant tumour by pathology; people with cancer pain of numerical pain score ≥ 7 during previous 24 hours; will not be treated with radiotherapy within 7 days prior to randomisation and during study; need chemotherapy, long-term administration of hormone, targeted therapy or bisphosphonates therapy should undergo a stable antitumour therapy prior to randomisation; patient or caregivers able to complete the questionnaires; ability to correctly understand and co-operate with medication guidance of doctors and nurses; no psychiatric problems; ECOG Performance Status ≤ 3; not participated in another clinical trial within 1 month before inclusion (including hydromorphone); voluntarily signed the informed consent Exclusion criteria: pain confirmed due to cause other than cancer; severe postoperative pain, paralytic ileus, brain metastasis, incoercible nausea or vomiting, cognitive dysfunction, severe depression, other conditions or reasons causing the patients unable to complete the clinical trial; hypersensitivity to opioids; abnormal laboratory results with obvious clinical significance, such as creatine ≥ 2 times upper limit of normal value, ALT or AST ≥ 2.5 times upper limit of normal value, or liver function of Child's C grade; cannot take drugs orally; received monoamine oxidase inhibitor within 2 weeks before randomisation; pregnant or lactating, or who plan to be pregnant within 1 month after the trial; opioid or alcohol addiction
Interventions	• PCA IV hydromorphone (continuous dose = 0) • PCA IV hydromorphone (continuous dose ≠ 0) • Oral morphine
Outcomes	Primary outcomes: mean pain score, number of breakthrough cancer pain episodes

NCT04243954 *(Continued)*

	Secondary outcomes: number of participants with a mean NRS pain score > 3, number of participants with a mean NRS pain score > 6, total dosage of opioids, satisfaction score, quality of life, number of participants who switched/discontinued therapy due to serious adverse events or lack of pain control
Starting date	28 January 2020
Contact information	Rongbo Lin, MD; Fujian Cancer Hospital
Notes	Last update posted: 5 March 2021; current status: completed.

NCT04296305

Study name	Effect of opioid infusion rate on abuse liability potential of intravenous hydromorphone for cancer pain
Methods	Allocation: randomised Endpoint classification: safety/efficacy study Intervention model: crossover assignment Blinding: quadruple Primary purpose: treatment
Participants	Moderate to severe cancer related pain Inclusion criteria: hospitalised people with diagnosis of cancer; moderate to severe cancer-related pain, defined as NRS pain score ≥ 4/10 at the time of study intervention; receiving no or only 'as needed' doses of opioids; normal cognitive status, defined as a normal state of arousal and an absence of obvious clinical findings of confusion, memory deficits or concentration deficits or a Memorial Delirium Assessment Scale score of < 13; ability to read and communicate in the English language; written informed consent from patient Exclusion criteria: contraindications to opioids, or history of opioid allergy; inability to secure IV access; known history or evidence of non-medical opioid use (e.g. abuse, misuse, addiction); oxygen saturations < 92% or respiratory rate < 12 breaths/minute on initial assessment; resting heart rate > 120 beats per minute on initial assessment; systolic blood pressure > 180 mmHg and < 90 mmHg or diastolic blood pressure > 100 mmHg or < 60 mmHg on initial assessment; receiving scheduled chronic opioid therapy (defined as the treatment of pain with opioids for ≥ 7 days); moderate to severe renal insufficiency (defined as glomerular filtration rate < 60 mL/minute/1.73 m^2); hepatic insufficiency (defined as ALT or AST > 3 times upper limit of normal or total bilirubin > 1.5 times upper limit of normal)
Interventions	• Hydromorphone • Placebo
Outcomes	Primary outcome: abuse liability potential of SH bolus vs FH bolus (from the "DRUG LIKING" scale of the DEQ questionnaire) Secondary outcomes: abuse liability potentials of SH bolus vs FH bolus (from the other scales of the DEQ questionnaire), analgesic efficacy, adverse effect, abuse liability potential among people who achieved successful analgesia, plasma concentration (Cmax) and peak (maximal) plasma concentration (Tmax) of hydromorphone metabolite H3G, elimination half-life of hydromorphone and its metabolite H3G, area-under-the-curve of hydromorphone and its metabolite H3G, metabolic ratio of H3G to hydromorphone, wild-type or single nucleotide polymorphisms in UGT enzymes in study population

NCT04296305 *(Continued)*

Starting date	5 March 2020
Contact information	Joseph A Arthur, +1 713 794 1649, jaarthur@mdanderson.org
Notes	Recruitment status: recruiting; estimated study completion date: 30 June 2021

ALT: alanine aminotransferase; AST: aspartate aminotransferase; DEQ: Drug Effects Questionnaire; ECOG: Eastern Cooperative Oncology Group; FH: fast IV hydromorphone; H3G: hydromorphone-3-glucuronide; IV: intravenous; NRS: numerical rating scale; PCA: participant-controlled analgesia; SH: slow IV hydromorphone; UGT: uridine 5'-diphospho-glucuronosyltransferase.

DATA AND ANALYSES

Comparison 1. Hydromorphone versus oxycodone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Participant-reported pain intensity (skewed data)	3		Other data	No numeric data
1.1.1 Visual analogue scale (VAS) endpoint pain intensity score (high score = poor outcome)	3		Other data	No numeric data
1.2 Specific adverse events	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.2.1 Somnolence	2	362	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.79, 1.57]
1.2.2 Nausea	3	622	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.74, 1.73]
1.2.3 Vomiting	3	622	Risk Ratio (M-H, Random, 95% CI)	1.18 [0.72, 1.94]
1.2.4 Dizziness	2	441	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.58, 1.44]
1.2.5 Constipation	3	622	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.72, 1.19]
1.2.6 Appetite loss	2	441	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.56, 1.93]
1.2.7 Diarrhoea	3	622	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.71, 1.50]
1.3 Serious adverse events	3	606	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.39, 1.00]
1.4 Leaving the study early	4	666	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.44, 1.38]

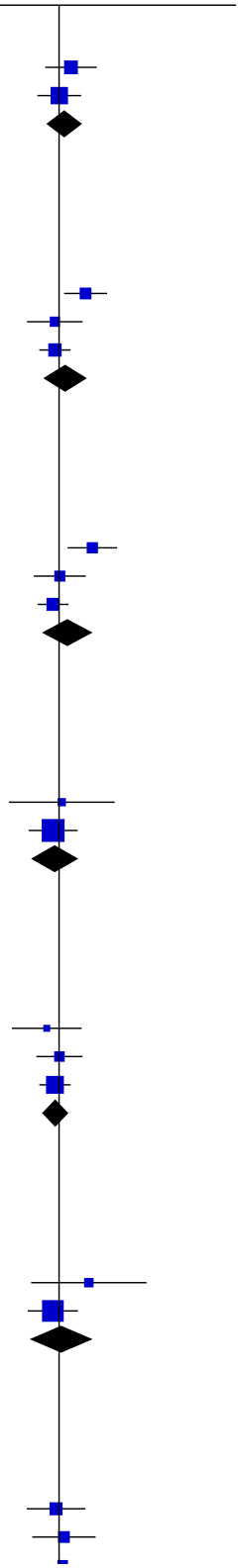
Analysis 1.1. Comparison 1: Hydromorphone versus oxycodone, Outcome 1: Participant-reported pain intensity (skewed data)

Participant-reported pain intensity (skewed data)

Study	Interventions	Mean	Standard deviation	n
Visual analogue scale (VAS) endpoint pain intensity score (high score = poor outcome)				
Hagen 1997	Hydromorphone	28.86	17.08	19
	Oxycodone	30.30	25.33	12
Inoue 2017	Hydromorphone	23.00	17.91	86
	Oxycodone	23.20	18.83	92
Inoue 2018	Hydromorphone	24.70	22.11	88
	Oxycodone	27.90	21.05	84

Analysis 1.2. Comparison 1: Hydromorphone versus oxycodone, Outcome 2: Specific adverse events

Study or Subgroup	Hydromorphone Events	Total	Oxycodone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.2.1 Somnolence						
Inoue 2017	23	88	19	93	41.9%	1.28 [0.75 , 2.18]
Inoue 2018	27	92	26	89	58.1%	1.00 [0.64 , 1.58]
Subtotal (95% CI)		**180**		**182**	**100.0%**	**1.11 [0.79 , 1.57]**
Total events:	50		45			
Heterogeneity: Tau² = 0.00; Chi² = 0.46, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 0.60 (P = 0.55)						
1.2.2 Nausea						
Inoue 2017	36	88	22	93	33.3%	1.73 [1.11 , 2.69]
Inoue 2018	18	92	19	89	26.6%	0.92 [0.52 , 1.63]
Yu 2014	45	130	49	130	40.1%	0.92 [0.66 , 1.27]
Subtotal (95% CI)		**310**		**312**	**100.0%**	**1.13 [0.74 , 1.73]**
Total events:	99		90			
Heterogeneity: Tau² = 0.09; Chi² = 5.59, df = 2 (P = 0.06); I² = 64%						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.2.3 Vomiting						
Inoue 2017	32	88	17	93	31.0%	1.99 [1.19 , 3.32]
Inoue 2018	21	92	20	89	29.9%	1.02 [0.59 , 1.74]
Yu 2014	45	130	51	130	39.0%	0.88 [0.64 , 1.21]
Subtotal (95% CI)		**310**		**312**	**100.0%**	**1.18 [0.72 , 1.94]**
Total events:	98		88			
Heterogeneity: Tau² = 0.13; Chi² = 7.14, df = 2 (P = 0.03); I² = 72%						
Test for overall effect: Z = 0.67 (P = 0.50)						
1.2.4 Dizziness						
Inoue 2017	6	88	6	93	17.6%	1.06 [0.35 , 3.15]
Yu 2014	23	130	26	130	82.4%	0.88 [0.53 , 1.47]
Subtotal (95% CI)		**218**		**223**	**100.0%**	**0.91 [0.58 , 1.44]**
Total events:	29		32			
Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.70)						
1.2.5 Constipation						
Inoue 2017	11	88	15	93	12.1%	0.78 [0.38 , 1.59]
Inoue 2018	25	92	24	89	27.6%	1.01 [0.62 , 1.63]
Yu 2014	45	130	49	130	60.3%	0.92 [0.66 , 1.27]
Subtotal (95% CI)		**310**		**312**	**100.0%**	**0.92 [0.72 , 1.19]**
Total events:	81		88			
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 2 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.2.6 Appetite loss						
Inoue 2017	7	88	4	93	22.9%	1.85 [0.56 , 6.10]
Yu 2014	22	130	25	130	77.1%	0.88 [0.52 , 1.48]
Subtotal (95% CI)		**218**		**223**	**100.0%**	**1.04 [0.56 , 1.93]**
Total events:	29		29			
Heterogeneity: Tau² = 0.06; Chi² = 1.26, df = 1 (P = 0.26); I² = 21%						
Test for overall effect: Z = 0.13 (P = 0.89)						
1.2.7 Diarrhoea						
Inoue 2017	16	88	18	93	38.8%	0.94 [0.51 , 1.72]
Inoue 2018	16	92	14	89	33.3%	1.11 [0.57 , 2.13]
Yu 2014	14	130	13	130	28.0%	1.08 [0.53 , 2.20]

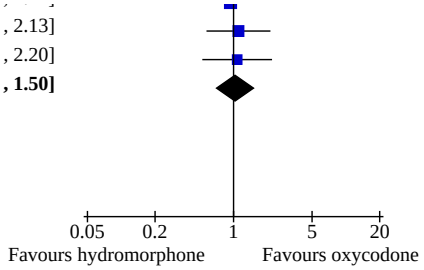


Analysis 1.2. (Continued)

Inoue 2018	16	92	14	89	33.3%	1.11 [0.57 , 2.13]
Yu 2014	14	130	13	130	28.0%	1.08 [0.53 , 2.20]
Subtotal (95% CI)		**310**		**312**	**100.0%**	**1.03 [0.71 , 1.50]**
Total events:	46		45			

Heterogeneity: Tau² = 0.00; Chi² = 0.15, df = 2 (P = 0.93); I² = 0%
Test for overall effect: Z = 0.15 (P = 0.88)

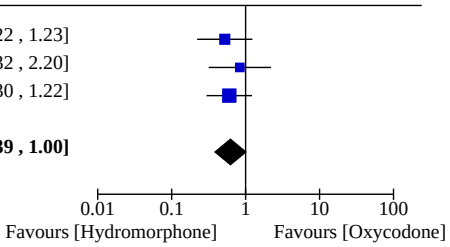
Test for subgroup differences: Chi² = 1.67, df = 6 (P = 0.95), I² = 0%



Analysis 1.3. Comparison 1: Hydromorphone versus oxycodone, Outcome 3: Serious adverse events

Study or Subgroup	Hydromorphone Events	Total	Oxycodone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Inoue 2017	7	88	14	92	30.7%	0.52 [0.22 , 1.23]
Inoue 2018	7	88	8	84	24.1%	0.84 [0.32 , 2.20]
Yu 2014	11	128	18	126	45.1%	0.60 [0.30 , 1.22]
Total (95% CI)		**304**		**302**	**100.0%**	**0.62 [0.39 , 1.00]**
Total events:	25		40			

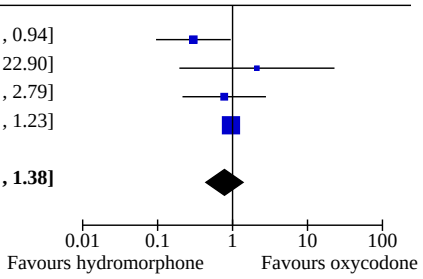
Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 1.94 (P = 0.05)
Test for subgroup differences: Not applicable



Analysis 1.4. Comparison 1: Hydromorphone versus oxycodone, Outcome 4: Leaving the study early

Study or Subgroup	Hydromorphone Events	Total	Oxycodone Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Hagen 1997	3	22	10	22	18.2%	0.30 [0.10 , 0.94]
Inoue 2017	2	88	1	93	5.3%	2.11 [0.20 , 22.90]
Inoue 2018	4	92	5	89	15.4%	0.77 [0.21 , 2.79]
Yu 2014	60	130	63	130	61.2%	0.95 [0.74 , 1.23]
Total (95% CI)		**332**		**334**	**100.0%**	**0.78 [0.44 , 1.38]**
Total events:	69		79			

Heterogeneity: Tau² = 0.12; Chi² = 4.34, df = 3 (P = 0.23); I² = 31%
Test for overall effect: Z = 0.86 (P = 0.39)
Test for subgroup differences: Not applicable



ADDITIONAL TABLES

Table 1. Comparison 2: hydromorphone versus oxycodone (pain intensity and adverse events from single study data)

Outcomes	Hydromorphone			Oxycodone			Difference		Study ID
	Mean	SD	n	Mean	SD	n	MD (95% CI)	P value	
Categorical pain intensity (ordinal scale) – at 7 days of treatment	1.5	0.4	19	1.4	0.3	12	0.10 (−0.15 to 0.35)	0.43	Hagen 1997
BPI (changed data) – at 28 days of maintenance therapy	−1.8	3.29	40	−1.7	3.91	41	−0.10 (−1.67 to 1.47)	0.90	Yu 2014
Specific adverse events – nausea – at 7 days of treatment	16.05	17.51	19	16.68	21.53	12	−0.63 (−15.13 to 13.87)	0.93	Hagen 1997
Specific adverse events – sedation – at 7 days of treatment	19.92	20.62	19	24.81	25.73	12	−4.89 (−22.15 to 12.37)	0.58	Hagen 1997

BPI: Brief Pain Inventory; CI: confidence interval; MD: mean difference; n: number of participants; SD: standard deviation.

Table 2. Comparison 2: hydromorphone versus oxycodone (adverse events and deaths from single study data)

Outcomes	Hydromorphone		Oxycodone		RR		Study ID
	Event n	Total n	Event n	Total n	RR (95% CI)	P value	
Specific adverse events – end of treatment (**ranged from 5 days of treatment to 28 days of maintenance therapy**)							
Abdominal discomfort	6	130	11	130	0.55 (0.21 to 1.43)	0.22	Yu 2014
Abdominal distension	9	130	11	130	0.82 (0.35 to 1.91)	0.64	Yu 2014
Anaemia	16	130	18	130	0.89 (0.47 to 1.67)	0.71	Yu 2014
Asthenia	13	130	13	130	1.00 (0.48 to 2.07)	1.00	Yu 2014
Bone marrow failure	11	130	13	130	0.85 (0.39 to 1.82)	0.43	Yu 2014
Chest discomfort	11	130	10	130	1.10 (0.48 to 2.50)	0.82	Yu 2014
Delirium	6	92	10	89	0.58 (0.22 to 1.53)	0.27	Inoue 2018

Table 2. Comparison 2: hydromorphone versus oxycodone (adverse events and deaths from single study data) *(Continued)*

Fever	7	88	6	93	1.23 (0.43 to 3.53)	0.70	Inoue 2017
Hyperhidrosis	5	130	12	130	0.42 (0.15 to 1.15)	0.09	Yu 2014
Malaise	3	88	7	93	0.45 (0.12 to 1.70)	0.24	Inoue 2017
Neutrophil count decreased	9	130	9	130	1.00 (0.41 to 2.44)	1.00	Yu 2014
Oedema peripheral	13	130	10	130	1.30 (0.59 to 2.86)	0.51	Yu 2014
Platelet count decreased	10	130	11	130	0.91 (0.40 to 2.07)	0.82	Yu 2014
Pyrexia	26	130	31	130	0.84 (0.53 to 1.33)	0.45	Yu 2014
Rash	9	130	8	130	1.13 (0.45 to 2.83)	0.80	Yu 2014
Urinary tract infection	6	130	11	130	0.55 (0.21 to 1.43)	0.22	Yu 2014
White blood cell count decreased	15	130	21	130	0.71 (0.39 to 1.32)	0.28	Yu 2014
Death – at 28 days of maintenance therapy							
All cause	8	130	16	130	0.5 (0.22 to 1.13)	0.09	Yu 2014

CI: confidence interval; n: number; RR: risk ratio.

Table 3. Comparison 3: hydromorphone versus morphine (participant-reported pain intensity: Brief Pain Inventory endpoint and visual analogue scale score from single study data)

Outcomes	Hydromorphone			Morphine			MD		Study ID
	Mean	SD	n	Mean	SD	n	MD (95% CI)	P value	
BPI – worst pain subscale score at 24 days of treatment	3.5	2.9	99	4.3	3.0	101	−0.80 (−1.62 to 0.02)	0.06	Hanna 2008
BPI – least pain subscale score at 24 days of treatment	1.8	2.0	99	1.8	2.0	101	0.00 (−0.55 to 0.55)	1.00	

Table 3. Comparison 3: hydromorphone versus morphine (participant-reported pain intensity: Brief Pain Inventory endpoint and visual analogue scale score from single study data) *(Continued)*

BPI – mean pain at 24 days of treatment	3.4	3.0	99	3.2	3.0	101	0.20 (−0.63 to 1.03)	0.64	
VAS –at week 1 of treatment	2.78	1.63	121	2.56	1.20	112	0.22 (−0.15 to 0.59)	0.25	Ma 2020
VAS –at week 2 of treatment	2.56	1.41	121	2.58	1.21	112	−0.02 (−0.36 to 0.32)	0.91	
VAS –at week 3 of treatment	2.48	1.28	121	2.62	1.24	112	−0.14 (−0.47 to 0.18)	0.39	
VAS –at week 4 of treatment	2.52	1.33	121	2.56	1.10	112	−0.04 (−0.35 to 0.27)	0.80	
VAS –at week 5 of treatment	2.40	1.34	121	2.63	1.13	112	−0.23 (−0.54 to 0.09)	0.17	
VAS –at week 6 of treatment	2.42	1.3	121	2.57	1.22	112	−0.16 (−0.48 to 0.17)	0.35	
VAS –at week 7 of treatment	2.51	1.25	121	2.53	1.07	112	−0.02 (−0.32 to 0.28)	0.88	
VAS –at week 8 of treatment	2.47	1.41	121	2.40	1.00	112	0.06 (−0.25 to 0.38)	0.69	
VAS –at week 9 of treatment	2.56	1.50	121	2.54	1.11	112	0.02 (−0.32 to 0.36)	0.91	
VAS –at week 10 of treatment	2.66	1.35	121	2.52	1.06	112	0.14 (−0.17 to 0.45)	0.38	
VAS –at week 11 of treatment	2.35	1.32	121	2.39	1.06	112	−0.04 (−0.34 to 0.27)	0.82	
VAS –at week 12 of treatment	2.22	1.22	121	2.37	1.03	112	−0.15 (−0.45 to 0.15)	0.34	

BPI: Brief Pain Inventory; CI: confidence interval; MD: mean difference; n: number of participants; SD: standard deviation; VAS: visual analogue scale.

Table 4. Comparison 3: hydromorphone versus morphine (pain relief rate 50% or greater, adverse events, leaving study early and death from single study data)

Outcome	Hydromorphone		Morphine		RR		Study ID
	n participants with events	Total n	n participants with events	Total n	RR (95% CI)	P value	
Participants improved at 84 days of treatment							

Table 4. Comparison 3: hydromorphone versus morphine (pain relief rate 50% or greater, adverse events, leaving study early and death from single study data) *(Continued)*

% of participants with pain relief rate ≥ 50%	85	121	79	112	1.00 (0.84 to 1.18)	0.962	Ma 2020
Specific adverse event –measured at 24 days of treatment							
Anaemia	25	99	21	101	1.21 (0.73 to 2.02)	0.45	Hanna 2008
Anorexia	24	99	20	101	1.22 (0.72 to 2.07)	0.45	
Anxiety	27	99	16	101	1.72 (0.99 to 2.99)	0.05	
Asthenia	28	99	19	101	1.50 (0.90 to 2.51)	0.12	
Constipation	52	99	34	101	1.56 (1.12 to 2.17)	0.009[a]	
Confusion	29	99	17	101	1.74 (1.02 to 2.96)	0.04[a]	
Dizziness	26	99	23	101	1.15 (0.71 to 1.88)	0.57	
Diarrhoea	29	99	17	101	1.74 (1.02 to 2.96)	0.04[a]	
Fatigue	26	99	21	101	1.26 (0.76 to 2.09)	0.36	
Headache	25	99	17	101	1.50 (0.87 to 2.60)	0.15	
Insomnia	27	99	19	101	1.45 (0.86 to 2.43)	0.16	
Nausea	37	99	40	101	0.94 (0.66 to 1.34)	0.75	
Oedema peripheral	23	99	23	101	1.02 (0.61 to 1.69)	0.94	
Pruritus	25	99	20	101	1.28 (0.76 to 2.14)	0.36	
Pyrexia	26	99	17	101	1.56 (0.90 to 2.69)	0.11	
Somnolence	30	99	27	101	1.13 (0.73 to 0.76)	0.58	
Vomiting	29	99	34	101	0.87 (0.58 to 1.31)	0.51	
Serious adverse event –measured at 24 days of treatment							

Table 4. Comparison 3: hydromorphone versus morphine (pain relief rate 50% or greater, adverse events, leaving study early and death from single study data) *(Continued)*

Serious adverse events	12	99	12	101	1.02 (0.48 to 2.16)	0.96	Hanna 2008
Adverse event measured during 84 days follow-up of treatment							
Constipation	26	121	37	112	0.65 (0.42 to 1.00)	0.05	Ma 2020
Leaving study early measured at 24 days of treatment							
Overall	39	99	28	101	1.42 (0.95 to 2.12)	0.08	Hanna 2008
Due to adverse events	15	99	11	101	1.39 (0.67 to 2.88)	0.37	
Due to lack of efficacy	11	99	4	101	2.81 (0.92 to 8.52)	0.07	
Leaving study early measured at 84 days of treatment							
Overall	108	121	103	112	0.97 (0.89 to 1.05)	0.48	Ma 2020
Due to discontinued intervention	25	121	26	112	0.89 (0.55 to 1.45)	0.64	
Due to lost to follow-up	8	121	9	112	0.82 (0.33 to 2.06)	0.68	
Due to change to other therapy	13	121	13	112	0.93 (0.45 to 1.91)	0.83	
Due to serious adverse events	4	121	4	112	0.93 (0.24 to 3.61)	0.91	
Death measured at 84 days of treatment							
All cause	58	121	51	112	1.05 (0.80 to 1.39)	0.71	Ma 2020
Death measured at 24 days of treatment							
All cause	0	99	3	101	0.15 (0.01 to 2.78)	0.2	Hanna 2008
Adverse events-treatment related occurred within 6 days of treatment	**Counts of reported events**	**Treatment related**	**Counts of reported events**	**Treatment related**	**—**	**—**	**Study ID**
Abdominal discomfort/pain	2	1	5	1	—	—	Moriarty 1999

Table 4. Comparison 3: hydromorphone versus morphine (pain relief rate 50% or greater, adverse events, leaving study early and death from single study data) *(Continued)*

Confusion	1	1	1	0	—	—
Constipation	1	1	2	1	—	—
Dizziness	2	2	2	2	—	—
Drowsiness	0	0	2	2	—	—
Fatigue	0	0	1	1	—	—
Nausea	3	2	2	0	—	—
Vomiting	3	1	2	0	—	—
Others	22	0	38	0	—	—
TOTAL	33	8	55	7	—	—

[a]Statistically significant P value.
CI: confidence interval; n: number; RR: risk ratio.

Table 5. Comparison 4: hydromorphone versus fentanyl (pain intensity: numerical rating scale pain scores)

Outcomes	Hydromorphone			Oxycodone			MD		Study ID
	Mean	SD	n	Mean	SD	n	MD (95% CI)	P value	
Pain ratings 60 minutes after treatment initiation (T0)									
Decrease from pain score at randomisation	4.90	2.31	40	5.14	2.16	42	−0.24 (−1.21 to 0.73)	0.63	Banala 2020
Decrease from maximum pain score of 10 for the IV hydromorphone group and from randomisation pain score for the IN fentanyl group	5.95	2.39	40	5.14	2.16	42	0.81 (−0.18 to 1.80)	0.11	

CI: confidence interval; IN: intranasal; IV: intravenous; MD: mean difference; n: number; SD: standard deviation.

Table 6. Comparison 4: hydromorphone versus fentanyl (leaving study early)

Outcome	Hydromorphone		Morphine		RR		Study ID
	n participants with events	Total n	n participants with events	Total n	RR (95% CI)	P value	
Overall	2	42	0	42	5.00 (0.24 to 101.11)	0.29	Banala 2020
Withdrew consent	1	42	0	42	3.00 (0.13 to 71.61)	0.50	
Ineligible due to abnormal electrocardiogram	1	42	0	42	3.00 (0.13 to 71.61)	0.50	

CI: confidence interval; n: number; RR: risk ratio.

APPENDICES

Appendix 1. Search strategies

CENTRAL (the Cochrane Library)

#1MeSH descriptor: [Hydromorphone] this term only

#2Hydromorphon*:ti,ab,kw (Word variations have been searched)

#3Dihydromorphinone:ti,ab,kw (Word variations have been searched)

#4Hydromorphon:ti,ab,kw (Word variations have been searched)

#5Palladone:ti,ab,kw (Word variations have been searched)

#6Laudacon:ti,ab,kw (Word variations have been searched)

#7Dilaudid:ti,ab,kw (Word variations have been searched)

#8#1 or #2 or #3 or #4 or #5 or #6 or #7

#9MeSH descriptor: [Neoplasms] this term only

#10neoplasm*:ti,ab,kw (Word variations have been searched)

#11malignan*:ti,ab,kw (Word variations have been searched)

#12tumour* or tumor*:ti,ab,kw (Word variations have been searched)

#13cancer*:ti,ab,kw (Word variations have been searched)

#14carcinoma*:ti,ab,kw (Word variations have been searched)

#15#9 or #10 or #11 or #12 or #13 or #14

#16MeSH descriptor: [Pain] explode all trees

#17MeSH descriptor: [Pain Measurement] this term only

#18MeSH descriptor: [Pain Threshold] this term only

#19Pain* or nocicept* or nocicept* or neuropath*:ti,ab,kw (Word variations have been searched)

#20#16 or #17 or #18 or #19

#21#8 and #15 and #20

MEDLINE (Ovid)

1. Hydromorphone/

2. Hydromorphon*.it,ab.

3. Dihydromorphinone.ti,ab.

4. Hydromorphon.ti,ab.

5. Palladone.ti,ab.

6. Laudacon.ti,ab.

7. Dilaudid.ti,ab.

8. or/1-7

9. NEOPLASMS*:ME

10. neoplasm*

11. malignan*

12. tumour* OR tumor*

13. cancer*

14. carcinoma*

15. or/9-14

16. exp Pain/

17. Pain Measurement/

18. Pain Threshold/

19. Pain* or nocicept* or nocicept* or neuropath*.ti.ab.

20. or/16-19

21. randomized controlled trial.pt.

22. controlled clinical trial.pt.

23. randomized.ti,ab. or randomised.ti,ab.

24. placebo.ti,ab.

25. drug therapy.fs.

26. randomly.ab.

27. trial.ab.

28. groups.ab.

29. or/21-28

30. (animals not (humans and animals)).sh.

31. 29 not 30

32. 8 and 15 and 20 and 31

Embase (Ovid)

1 Hydromorphone/

2 Hydromorphon*.ti,ab.

3 Dihydromorphinone.ti,ab.

4 Hydromorphon.ti,ab.

5 Palladone.ti,ab.

6 Laudacon.ti,ab.

7 Dilaudid.ti,ab.

8 or/1-7

9 NEOPLASMS/

10 neoplasm*.tw.

11 malignan*.tw.

12 (tumour* or tumor*).tw.

13 cancer*.tw.

14 carcinoma*.tw.

15 or/9-14

16 exp Pain/

17 Pain Measurement/

18 Pain Threshold/

19 (Pain* or nocicept* or nocicept* or neuropath*).tw.

20 or/16-19

21 random$.tw.

22 factorial$.tw.

23 crossover$.tw.

24 cross over$.tw.

25 cross-over$.tw.

26 placebo$.tw.

27 (doubl$ adj blind$).tw.

28 (singl$ adj blind$).tw.

29 assign$.tw.

30 allocat$.tw.

31 volunteer$.tw.

32 Crossover Procedure/

33 double-blind procedure.tw.

34 Randomized Controlled Trial/

35 Single Blind Procedure/

36 or/21-35

37 (animal/ or nonhuman/) not human/

38 36 not 37

39 8 and 15 and 20 and 38

Appendix 2. Search strategies (2019 update)

CENTRAL (CRSO)*

#1 MESH DESCRIPTOR Hydromorphone 312

#2 Hydromorphon*:TI,AB,KY 680

#3 Dihydromorphinone:TI,AB,KY 6

#4 Hydromorphon:TI,AB,KY 3

#5 Palladone:TI,AB,KY 1

#6 Laudacon:TI,AB,KY 0

#7 Dilaudid:TI,AB,KY 34

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 701

#9 MESH DESCRIPTOR Neoplasms 5302

#10 neoplasm*:TI,AB,KY 65280

#11 malignan*:TI,AB,KY 13987

#12 (tumour* or tumor*):TI,AB,KY 47206

#13 cancer*:TI,AB,KY 108333

#14 carcinoma*:TI,AB,KY 30345

#15 #9 OR #10 OR #11 OR #12 OR #13 OR #14 150590

#16 MESH DESCRIPTOR pain EXPLODE ALL TREES 42571

#17 MESH DESCRIPTOR Pain Measurement 19542

#18 MESH DESCRIPTOR Pain Threshold 1553

#19 (Pain* or nocicept* or nocicept* or neuropath*):TI,AB,KY 128038

#20 #8 OR #16 OR #17 OR #18 OR #19 133854

#21 #8 AND #15 AND #20 80

#22 06/04/2016 TO 29/01/2019:CD 380721

#23 #21 AND #22 39

MEDLINE (Ovid)

1 Hydromorphone/ (1206)

2 Hydromorphon*.ti,ab. (1466)

3 Dihydromorphinone.ti,ab. (39)

4 Hydromorphon.ti,ab. (2)

5 Palladone.ti,ab. (6)

6 Laudacon.ti,ab. (0)

7 Dilaudid.ti,ab. (73)

8 or/1-7 (2010)

9 NEOPLASMS/ (394359)

10 neoplasm*.tw. (126864)

11 malignan*.tw. (529505)

12 (tumour* or tumor*).tw. (1558218)

13 cancer*.tw. (1591996)

14 carcinoma*.tw. (612732)

15 or/9-14 (3070335)

16 exp Pain/ (369037)

17 Pain Measurement/ (79733)

18 Pain Threshold/ (12115)

19 (Pain* or nocicept* or nocicept* or neuropath*).tw. (738677)

20 or/16-19 (886784)

21 randomized controlled trial.pt. (475140)

22 controlled clinical trial.pt. (92878)

23 randomized.ab. (436334)

24 placebo.ab. (196004)

25 drug therapy.fs. (2078971)

26 randomly.ab. (306579)

27 trial.ab. (455584)

28 or/21-27 (2971049)

29 exp animals/ not humans.sh. (4540309)

30 28 not 29 (2658328)

31 8 and 15 and 20 and 30 (221)

32 (201604* or 201605* or 201606* or 201607* or 201608* or 201609* or 201610* or 201611* or 201612* or 2017* or 2018* or 2019*).ed. (2777020)

33 31 and 32 (31)

Embase (Ovid)

1 Hydromorphone/ (8949)

2 Hydromorphon*.ti,ab. (2464)

3 Dihydromorphinone.ti,ab. (42)

4 Hydromorphon.ti,ab. (8)

5 Palladone.ti,ab. (9)

6 Laudacon.ti,ab. (0)

7 Dilaudid.ti,ab. (165)

8 or/1-7 (9243)

9 NEOPLASMS/ (39324)

10 neoplasm*.tw. (160849)

11 malignan*.tw. (718165)

12 (tumour* or tumor*).tw. (2030835)

13 cancer*.tw. (2191887)

14 carcinoma*.tw. (784821)

15 or/9-14 (3854947)

16 exp Pain/ (1189016)

17 Pain Measurement/ (6263)

18 Pain Threshold/ (16758)

19 (Pain* or nocicept* or nocicept* or neuropath*).tw. (1050432)

20 or/16-19 (1628555)

21 random$.tw. (1374887)

22 factorial$.tw. (34325)

23 crossover$.tw. (68975)

24 cross over$.tw. (30200)

25 cross-over$.tw. (30200)

26 placebo$.tw. (284357)

27 (doubl$ adj blind$).tw. (194809)

28 (singl$ adj blind$).tw. (22305)

29 assign$.tw. (355385)

30 allocat$.tw. (135404)

31 volunteer$.tw. (240077)

32 Crossover Procedure/ (58051)

33 double-blind procedure.tw. (228)

34 Randomized Controlled Trial/ (533658)

35 Single Blind Procedure/ (33782)

36 or/21-35 (2095718)

37 (animal/ or nonhuman/) not human/ (5315020)

38 36 not 37 (1857908)

39 8 and 15 and 20 and 38 (233)

40 (201604* or 201605* or 201606* or 201607* or 201608* or 201609* or 201610* or 201611* or 201612* or 2017* or 2018* or 2019*).dd. (2701641)

41 39 and 40 (20)

*CRSO – Cochrane Register of Studies/Cochrane Central Register of Controlled Trials

Appendix 3. Search strategies (2019–2020 update)

CENTRAL (CRSO)*

#1 MESH DESCRIPTOR Hydromorphone

#2 Hydromorphon*:TI,AB,KY

#3 Dihydromorphinone:TI,AB,KY

#4 Hydromorphon:TI,AB,KY

#5 Palladone:TI,AB,KY

#6 Laudacon:TI,AB,KY

#7 Dilaudid:TI,AB,KY

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 MESH DESCRIPTOR Neoplasms

#10 neoplasm*:TI,AB,KY

#11 malignan*:TI,AB,KY

#12 (tumour* or tumor*):TI,AB,KY

#13 cancer*:TI,AB,KY

#14 carcinoma*:TI,AB,KY

#15 #9 OR #10 OR #11 OR #12 OR #13 OR #14

#16 MESH DESCRIPTOR pain EXPLODE ALL TREES

#17 MESH DESCRIPTOR Pain Measurement

#18 MESH DESCRIPTOR Pain Threshold

#19 (Pain* or nocicept* or nocicept* or neuropath*):TI,AB,KY

#20 #8 OR #16 OR #17 OR #18 OR #19

#21 #8 AND #15 AND #20

#22 06/04/2016 TO 23/11/20209:CD

#23 #21 AND #22

MEDLINE (Ovid)

1 Hydromorphone/

2 Hydromorphon*.tw

3 Dihydromorphinone.tw

4 Hydromorphon.tw

5 Palladone.tw

6 Laudacon.tw

7 Dilaudid.tw

8 or/1-7

9 NEOPLASMS/

10 neoplasm*.tw.

11 malignan*.tw.

12 (tumour* or tumor*).tw.

13 cancer*.tw.

14 carcinoma*.tw.

15 or/9-14

16 exp Pain/

17 Pain Measurement/

18 Pain Threshold/

19 (Pain* or nocicept* or nocicept* or neuropath*).tw.

20 or/16-19

21 randomized controlled trial.pt.

22 controlled clinical trial.pt.

23 randomized.ab.

24 placebo.ab.

25 drug therapy.fs.

26 randomly.ab.

27 trial.ab.

28 or/21-27

29 exp animals/ not humans.sh.

30 28 not 29

31 8 and 15 and 20 and 30

32 (201604* or 201605* or 201606* or 201607* or 201608* or 201609* or 201610* or 201611* or 201612* or 2017* or 2018* or 2019* or 2020*).ed.

33 31 and 32

EMBASE (Ovid)

1 Hydromorphone/

2 Hydromorphon*.tw

3 Dihydromorphinone.tw

4 Hydromorphon.tw

5 Palladone.tw

6 Laudacon.tw

7 Dilaudid.tw

8 or/1-7

9 NEOPLASMS/

10 neoplasm*.tw.

11 malignan*.tw.

12 (tumour* or tumor*).tw.

13 cancer*.tw.

14 carcinoma*.tw.

15 or/9-14

16 exp Pain/

17 Pain Measurement/

18 Pain Threshold/

19 (Pain* or nocicept* or nocicept* or neuropath*).tw.

20 or/16-19

21 random$.tw.

22 factorial$.tw.

23 crossover$.tw.

24 cross over$.tw.

25 cross-over$.tw.

26 placebo$.tw.

27 (doubl$ adj blind$).tw.

28 (singl$ adj blind$).tw.

29 assign$.tw.

30 allocat$.tw.

31 volunteer$.tw.

32 Crossover Procedure/

33 double-blind procedure.tw.

34 Randomized Controlled Trial/

35 Single Blind Procedure/

36 or/21-35

37 (animal/ or nonhuman/) not human/

38 36 not 37

39 8 and 15 and 20 and 38

40 (201604* or 201605* or 201606* or 201607* or 201608* or 201609* or 201610* or 201611* or 201612* or 2017* or 2018* or 2019* or 2020*).dd.

41 39 and 40

*CRSO – Cochrane Register of Studies/Cochrane Central Register of Controlled Trials

WHAT'S NEW

Date	Event	Description
23 November 2020	New search has been performed	This review was updated to include the results of a new search in November 2020.
23 November 2020	New citation required but conclusions have not changed	Update identified four new studies (an additional 669 participants). No major changes to GRADE assessment.

HISTORY

Protocol first published: Issue 5, 2014
Review first published: Issue 10, 2016

CONTRIBUTIONS OF AUTHORS

Protocol development: all authors contributed equally.

Study screening: YL, LY, ZD, ST.

Data extraction: LY, ZD.

Data analysis: YL, GL, RK.

Report writing: YJB, RK, JX, ST, JM.

Future update: all authors in the existing team will be responsible for future updates.

DECLARATIONS OF INTEREST

YL: none; YL is a physiologist, anaesthesiologist and pain doctor.

JM: none; JM is an anaesthesiologist and pain doctor.

GL: none; GL is a psychologist and pain doctor.

ZD: none; ZD is a pain doctor.

RK: none; RK is a pharmacist and manages people with pain.

JX: none.

SZ: none.

STD: none.

YLiq: none; YLiq is a pain doctor.

The previous version of this review was identified in a 2019 audit as not meeting the current definition of the Cochrane Commercial Sponsorship policy. At the time of its publication it was compliant with the interpretation of the existing policy. A new author team fully compliant with the 2014 policy completed the update.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- Beijing Municipal Administration of Hospitals Clinical Medicine Development of Special Funding Support [ZYLX201810], China
- National Natural Science Foundation of China (81800765), China
- Beijing Municipal Science & Technology Commission,China (Z191100006619044), China
- The funding support of creating excellent talent of Jizhou, China (2019001), China
- China Postdoctoral Science Foundation (2019M650769), China

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made some amendments for the unit of analysis issues. In our protocol, we stated that we would only include RCTs that randomised the individual participant but did not include any plans for dealing with data from cross-over RCTs. At review stage, we encountered this type of RCT. To avoid carry-over effects, we only used data from the first phase of the study. The orriginal published protocol did not mention timepoints. Given that cancer pain is a type of chronic pain, the assessment or observation timepoint of effectiveness and safety outcomes of opioids is quite random. Therefore in this update, we included and extracted all eligible RCTs that reported outcomes at any timepoints.

NOTES

This review replaces the original review 'Hydromorphone for acute and chronic pain' as the original author team were unavailable to complete the update (Quigley 2013, withdrawn). This review focuses on cancer pain only and adheres to current Cochrane standards.

INDEX TERMS

Medical Subject Headings (MeSH)

Analgesics, Opioid [adverse effects]; *Cancer Pain [drug therapy]; Hydromorphone [adverse effects]; Morphine [adverse effects]; *Neoplasms [complications]; Oxycodone

MeSH check words

Adult; Child; Humans; Male; Middle Aged